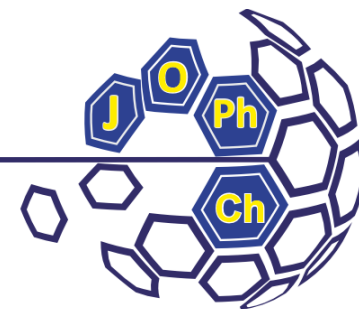


## Supporting Information

<https://doi.org/10.24959/ophcj.26.360150>

Freely available online on  
<http://ophcj.nuph.edu.ua>

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## Determination of Masked Basicity in Imidazo[1,5-a]pyridine Carboxylic Acids Using Esters

S. V. Stetsenko<sup>1,2</sup>, G. P. Grabchuk<sup>1</sup>

<sup>1</sup> *Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., 01033 Kyiv, Ukraine*

<sup>2</sup> *Enamine Ltd, 78 Winston Churchill str., 02094 Kyiv, Ukraine*

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**Table S1.** Compounds characterization

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## S1. Potentiometric titration and pKa determination

The pK<sub>a</sub> values of the investigated imidazo[1,5-*a*]pyridine carboxylic acids, esters, and hydrochlorides were determined by potentiometric titration using a TitroLine® 7000 automatic titrator (SI Analytics/Xylem). The measurements were performed under potentiometric titration conditions with continuous stirring [S1].

Carboxylic acids and hydrochlorides were titrated with standardized aqueous NaOH. Neutral ester derivatives, whose basic-center pK<sub>a</sub> values lie below pH 7, were titrated with standardized aqueous HCl. The concentrations used for the calculations were C<sub>NaOH</sub> = 0.09910 M and C<sub>HCl</sub> = 0.10967 M.

A sample of the corresponding compound was dissolved or suspended in distilled water (V<sub>0</sub> = 47.5 mL), and the solution was titrated by incremental addition of the appropriate titrant. The pH was recorded after stabilization at each titration point. The exact sample masses, titrant volumes, pH values, and pointwise pK<sub>a</sub> calculations are provided in **Table S2**.

For the titration of carboxylic acids with NaOH, the concentrations of the acid and conjugate base forms were calculated as:

$$[HA] = \frac{\left(n - \frac{C_{NaOH}V_{NaOH}}{1000}\right) 1000}{V_0 + V_{NaOH}}$$
$$[A^-] = \frac{n1000}{V_0 + V_{NaOH}} - [HA]$$
$$pK_a = pH + \log\left(\frac{[HA]}{[A^-]}\right)$$

For titration of neutral ester bases with HCl, the concentrations of the free base and protonated form were calculated as:

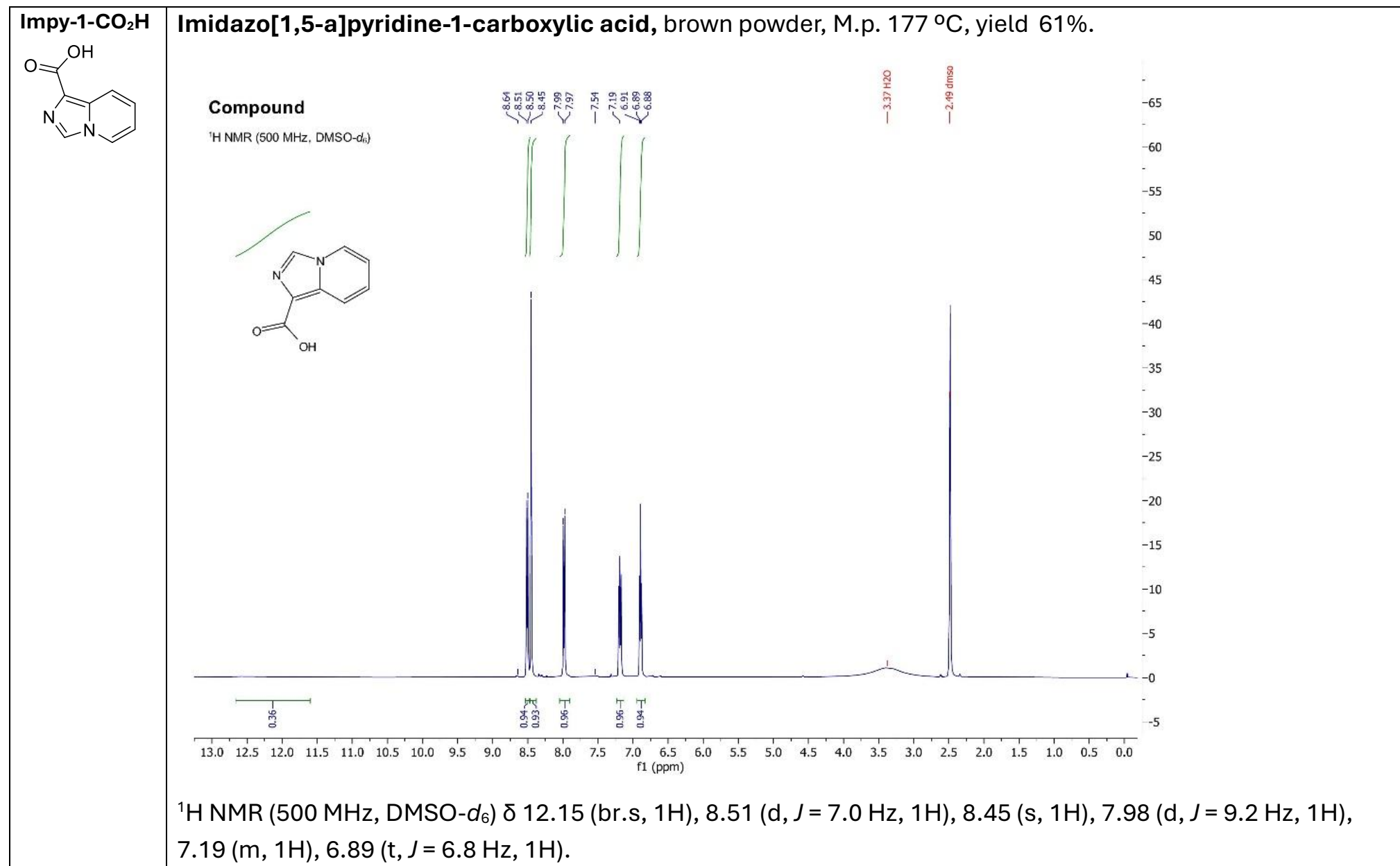
$$[B] = \frac{\left(n - \frac{C_{HCl}V_{HCl}}{1000}\right) 1000}{V_0 + V_{HCl}}$$
$$[BH^+] = \frac{n1000}{V_0 + V_{HCl}} - [B]$$
$$pK_a(BH^+) = pH + \log\left(\frac{[BH^+]}{[B]}\right)$$

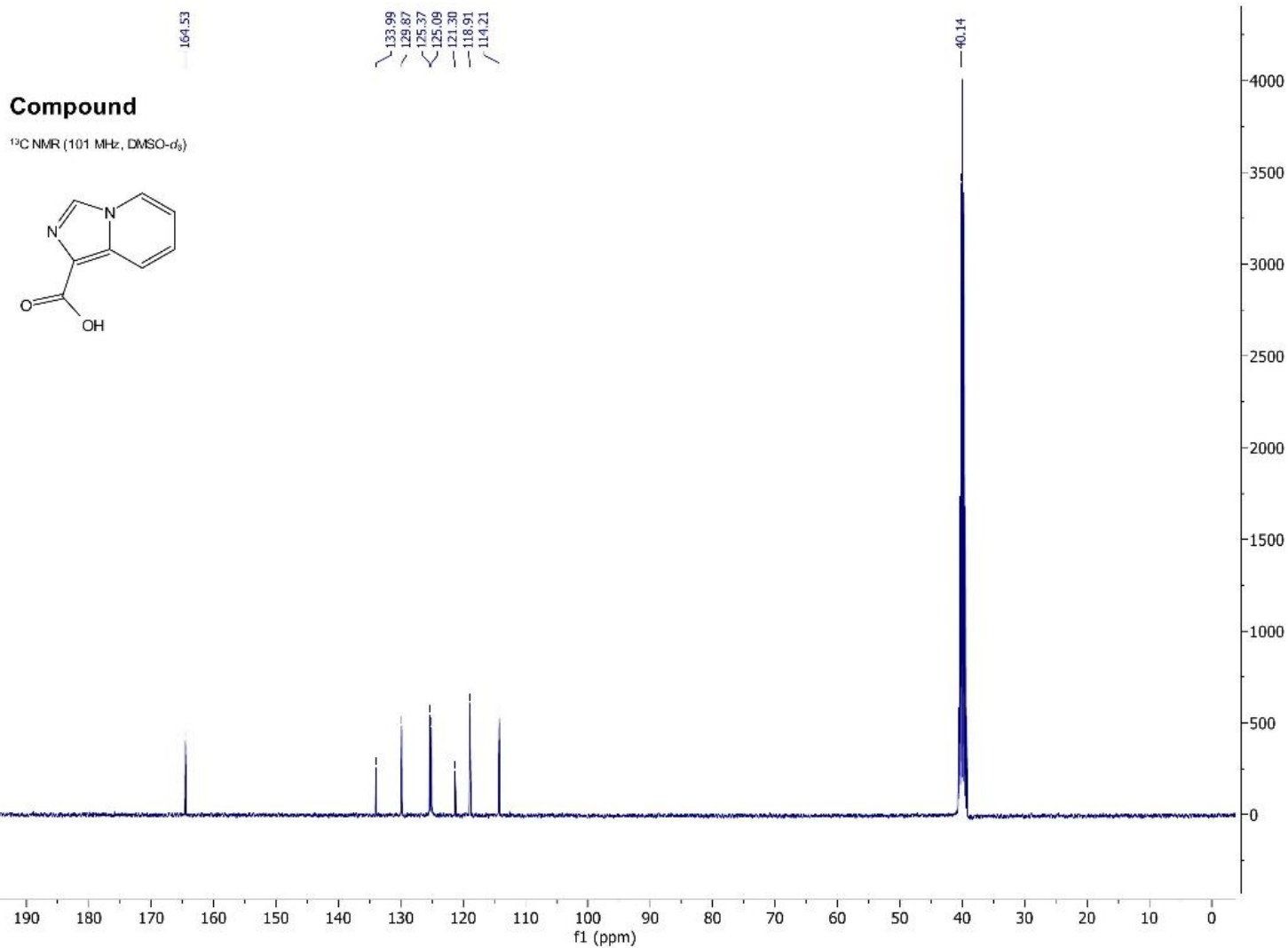
Only points from the buffer regions of the titration curves were used for averaging. Points close to the beginning of the titration and points near or after the equivalence region were excluded when they showed unstable or non-buffer behavior. The reported pK<sub>a</sub> values are arithmetic means of the accepted pointwise pK<sub>a</sub> values.

The full set of titration curves is provided in **Table S2**.

[S1] **Pashko, M. O.; Granat, D. S.; Klymenko-Ulianov, O. O.; Leha, D. O.; Yagupolskii, Y. L.; Ryabukhin, S. V.; Volochnyuk, D. M.** Supporting Information for “Difluoro(methoxy)methyl Is a Neglected Group for Medicinal Chemistry—Revival via CF<sub>2</sub>OMe-Containing Amines.” *Org. Lett.* **2026**, Article ASAP. <https://doi.org/10.1021/acs.orglett.5c05426.s001>

**Table S1.** Compounds characterization

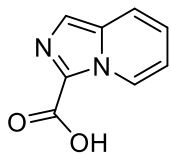




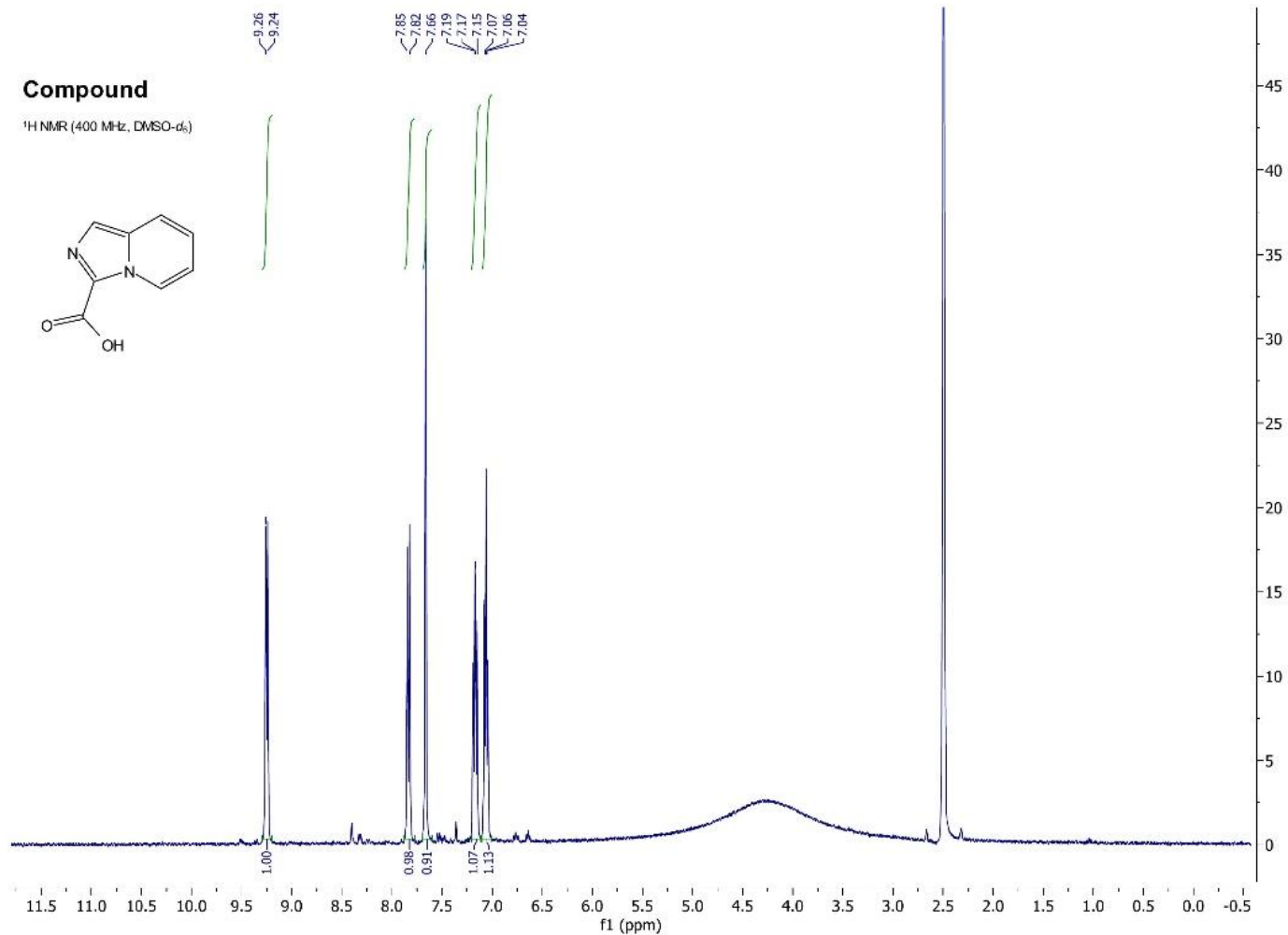
<sup>13</sup>C NMR (101 MHz, dmsO)  $\delta$  164.5, 134.0, 129.9, 125.4, 125.1, 121.3, 118.9, 114.2.

LCMS, positive mode,  $m/z$ : 163.0 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 162.0429; found: 162.0428.

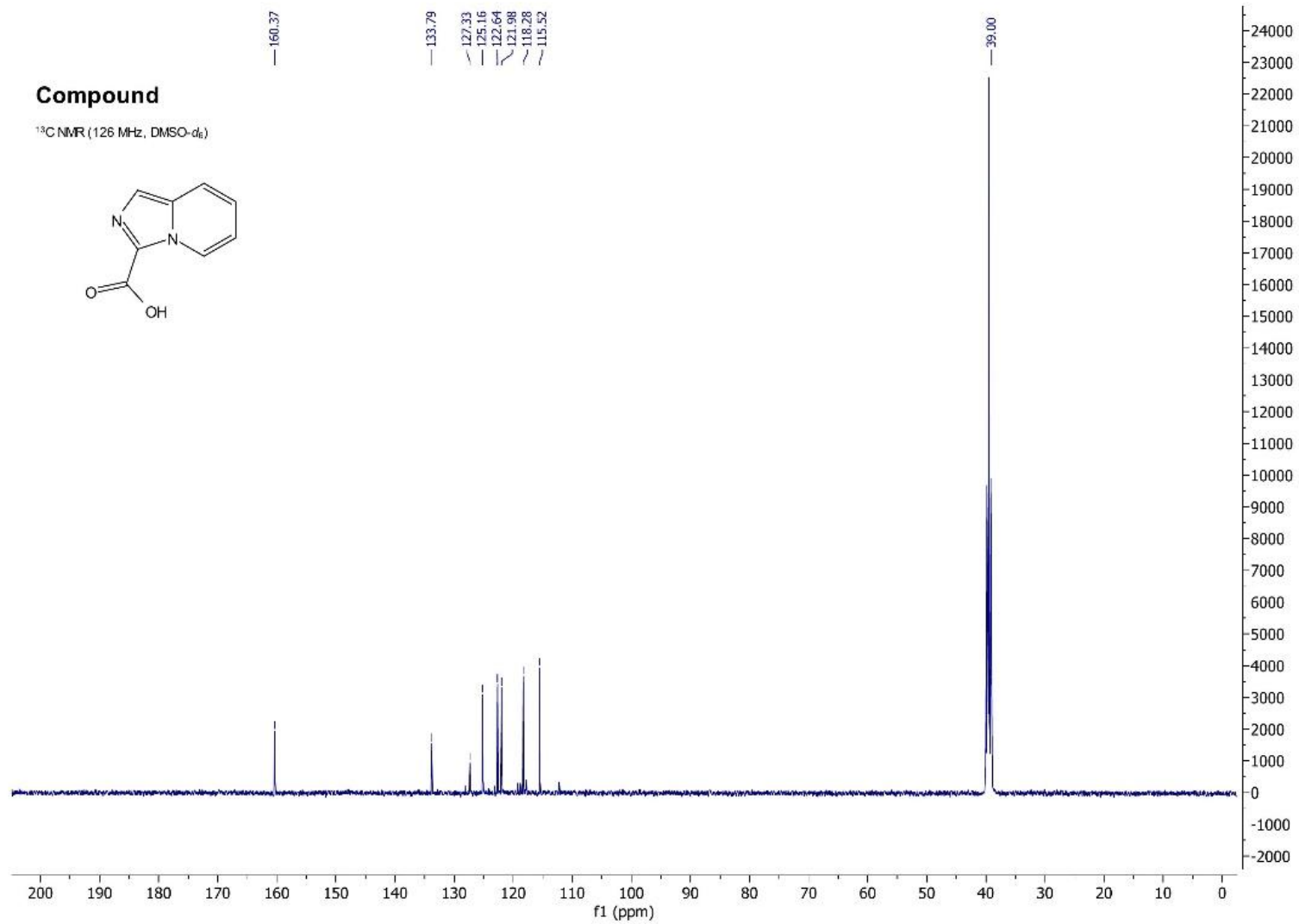
Impy-3-CO<sub>2</sub>H



Imidazo[1,5-a]pyridine-3-carboxylic acid, light-brown powder, M.p. 124 °C, yield 43%.



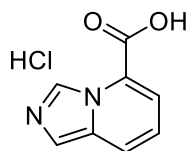
<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 9.25 (d, *J* = 7.0 Hz, 1H), 7.83 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.66 (s, 1H), 7.20 – 7.13 (m, 1H), 7.06 (t, *J* = 6.9 Hz, 1H), -COOH was not observed.



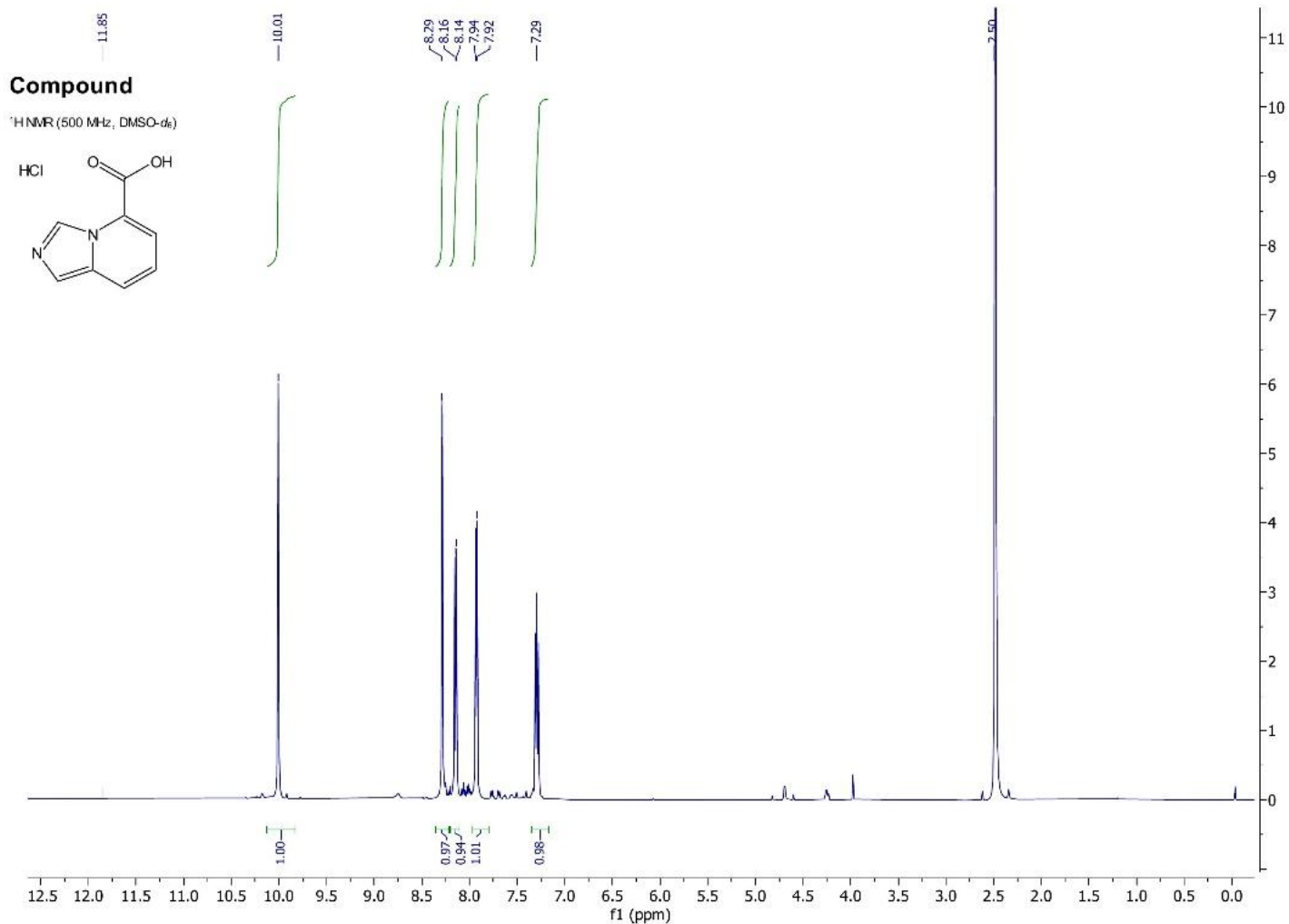
<sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>) δ 160.4, 133.8, 127.3, 125.2, 122.6, 122.0, 118.3, 115.5.

LCMS, positive mode, m/z: 163.2 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 162.0429; found: 162.0426.

Impy-5-  
CO<sub>2</sub>H·HCl



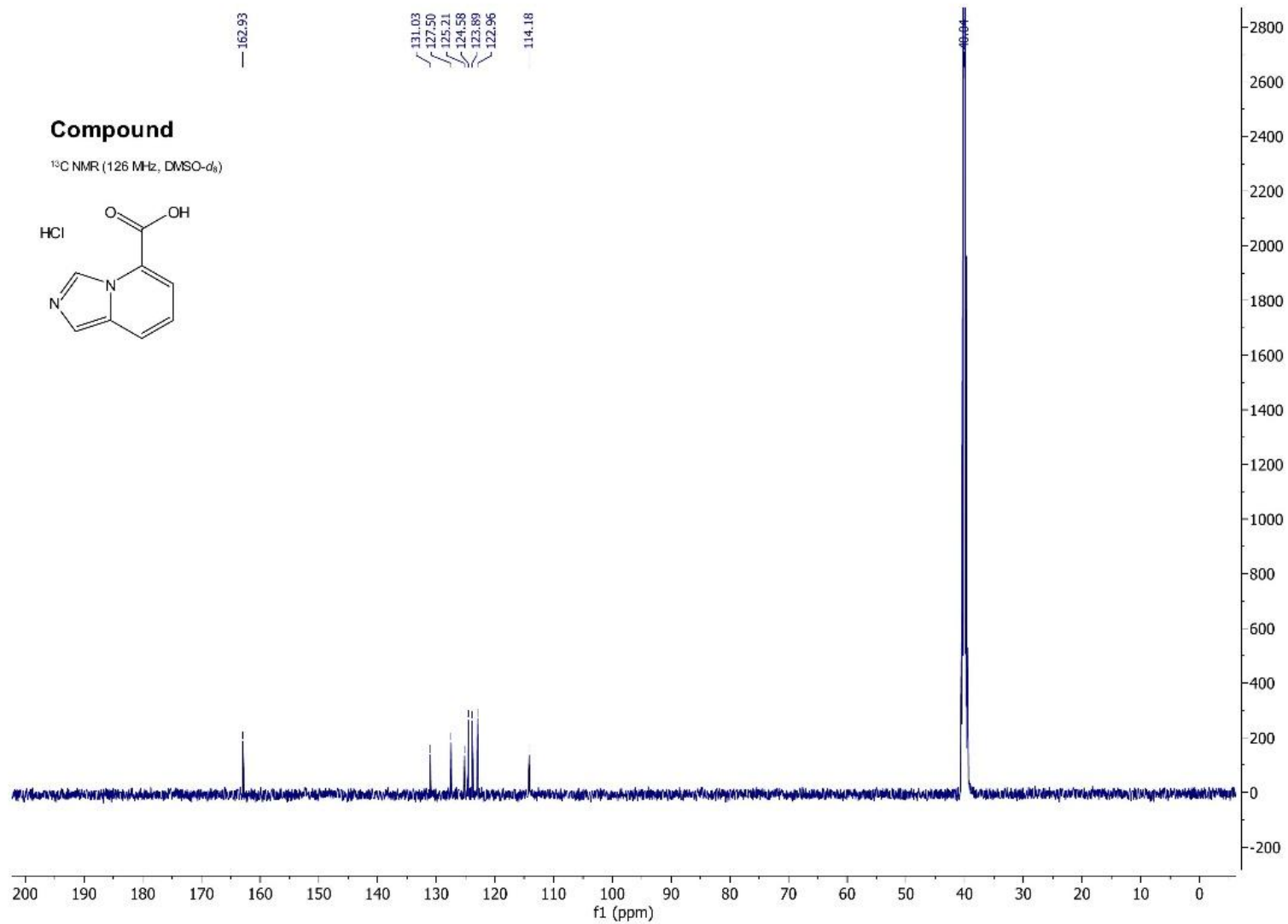
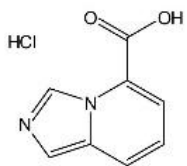
Imidazo[1,5-a]pyridine-5-carboxylic acid hydrochloride, brown powder, M.p. above 196 °C, yield 54%.



<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 10.01 (s, 1H), 8.29 (s, 1H), 8.15 (d, *J* = 9.2 Hz, 1H), 7.93 (d, *J* = 7.0 Hz, 1H), 7.29 (dd, *J* = 9.2, 7.0 Hz, 1H), -COOH was not observed.

### Compound

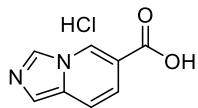
<sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>)



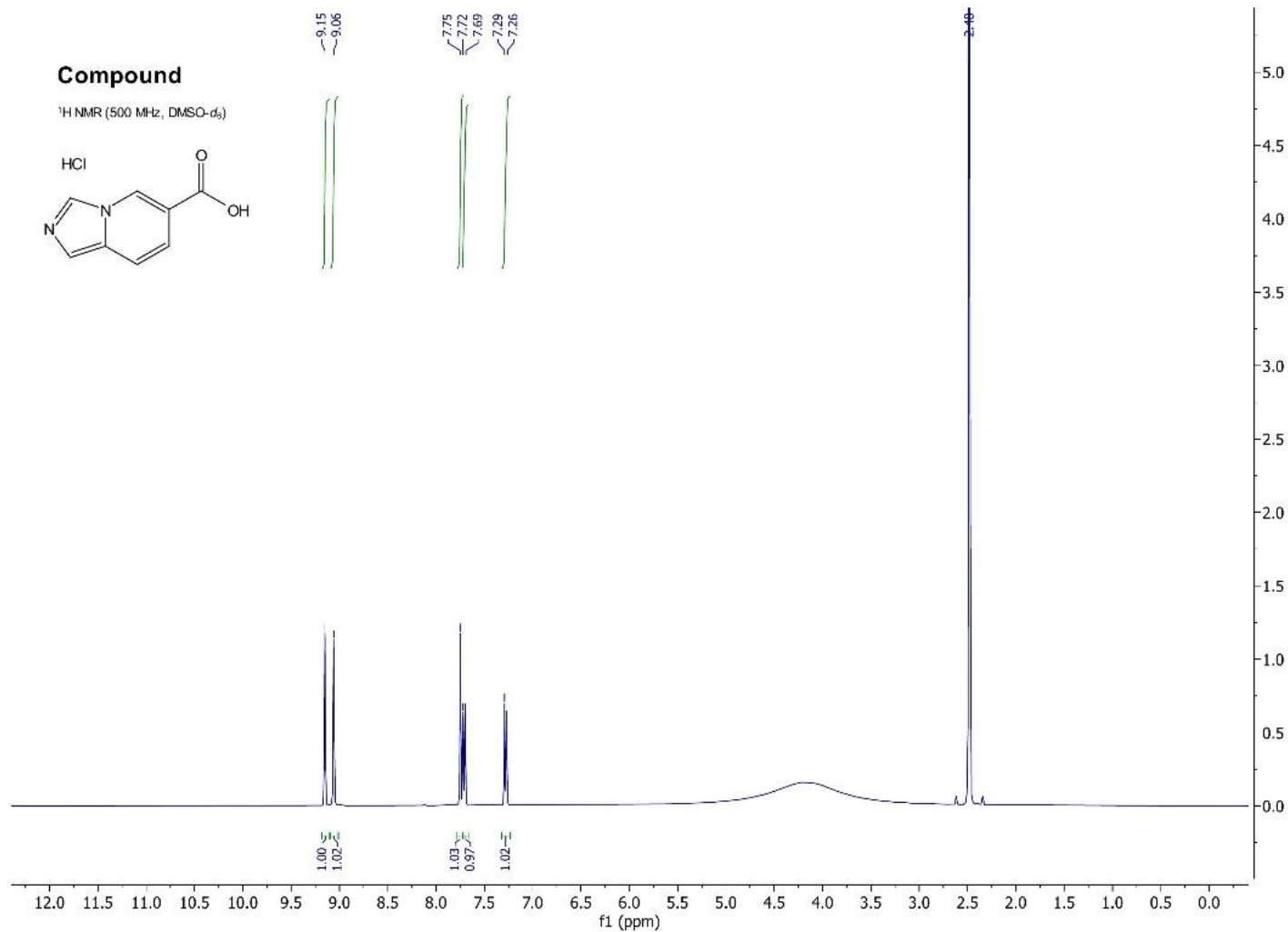
<sup>13</sup>C NMR (126 MHz, DMSO)  $\delta$  162.9, 131.0, 127.5, 125.2, 124.6, 123.9, 123.0, 114.2.

LCMS, positive mode,  $m/z$ : 163.0  $[M+H]^+$ . HRMS (ESI): calcd. for  $C_8H_6N_2O_2$   $[M+H]^+$ : 162.0429; found: 162.0428.

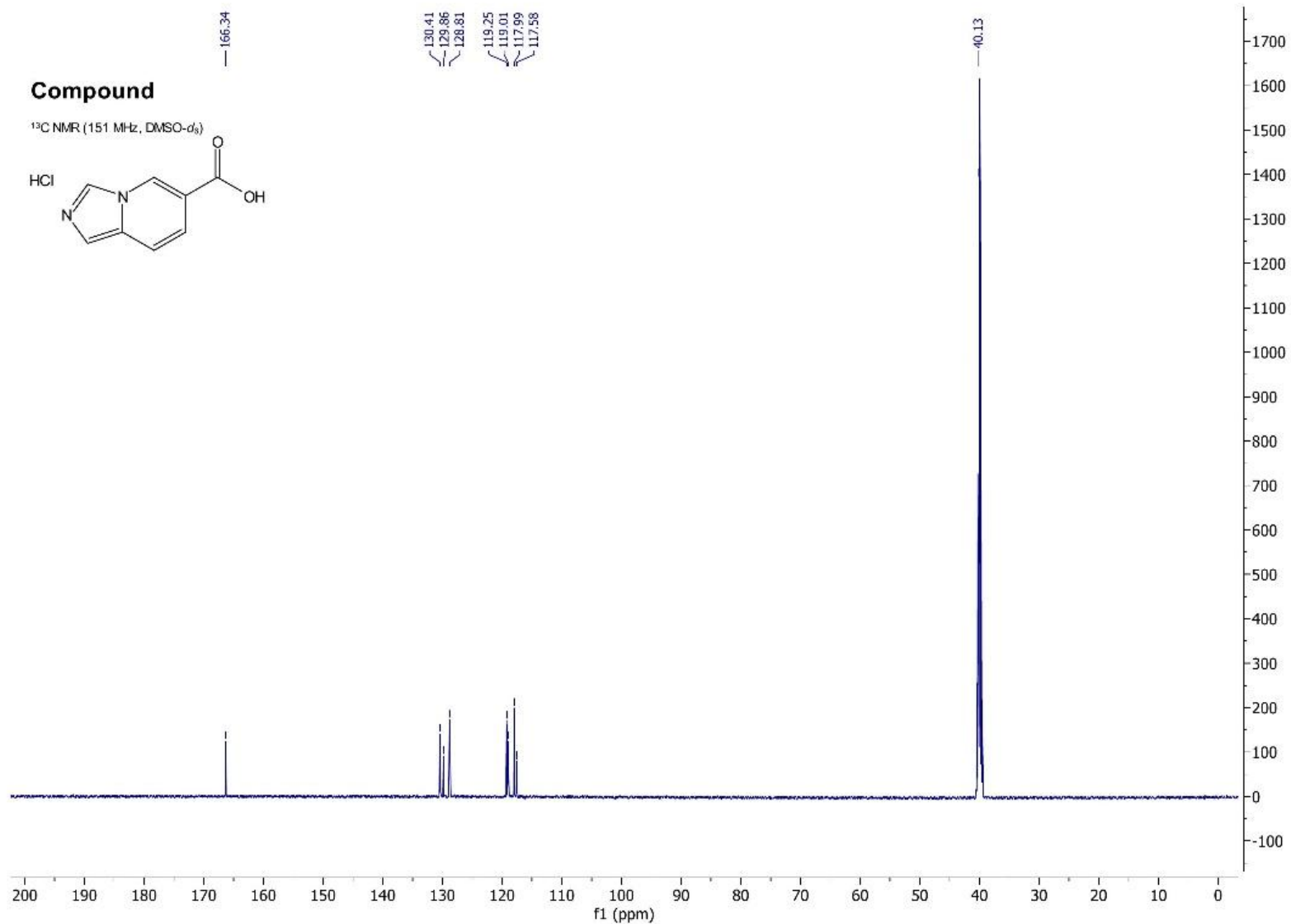
Impy-6-  
CO<sub>2</sub>H·HCl



Imidazo[1,5-a]pyridine-6-carboxylic acid hydrochloride, brown powder, M.p. above 210 °C.



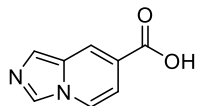
<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.15 (s, 1H), 9.06 (s, 1H), 7.75 (s, 1H), 7.71 (d, *J* = 9.6 Hz, 1H), 7.28 (d, *J* = 9.6 Hz, 1H), -COOH was not observed.



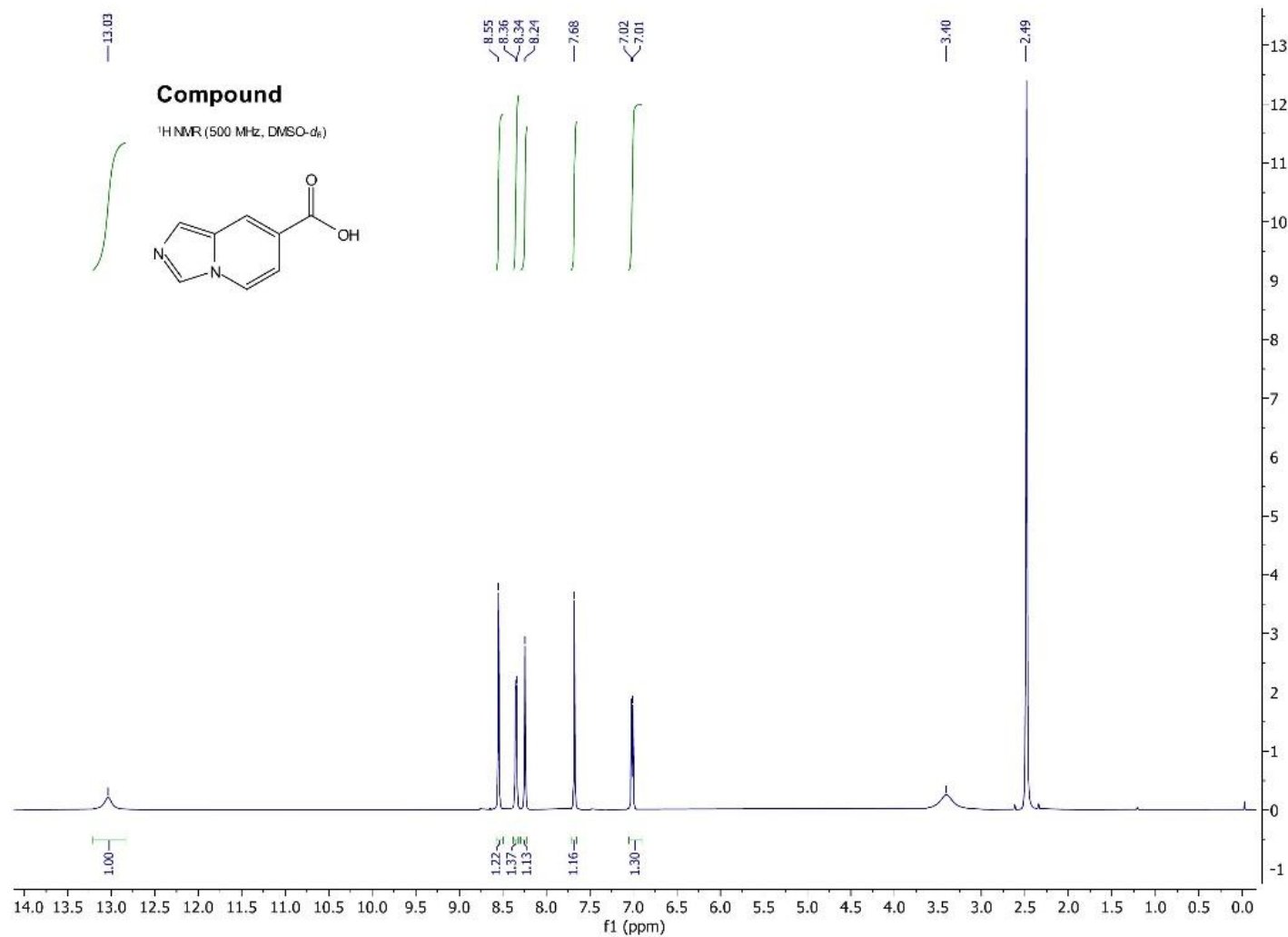
<sup>13</sup>C NMR (151 MHz, dmsO)  $\delta$  166.3, 130.4, 129.9, 128.8, 119.3, 119.0, 118.0, 117.6.

LCMS, positive mode, m/z: 163.0 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 162.0429; found: 162.0429.

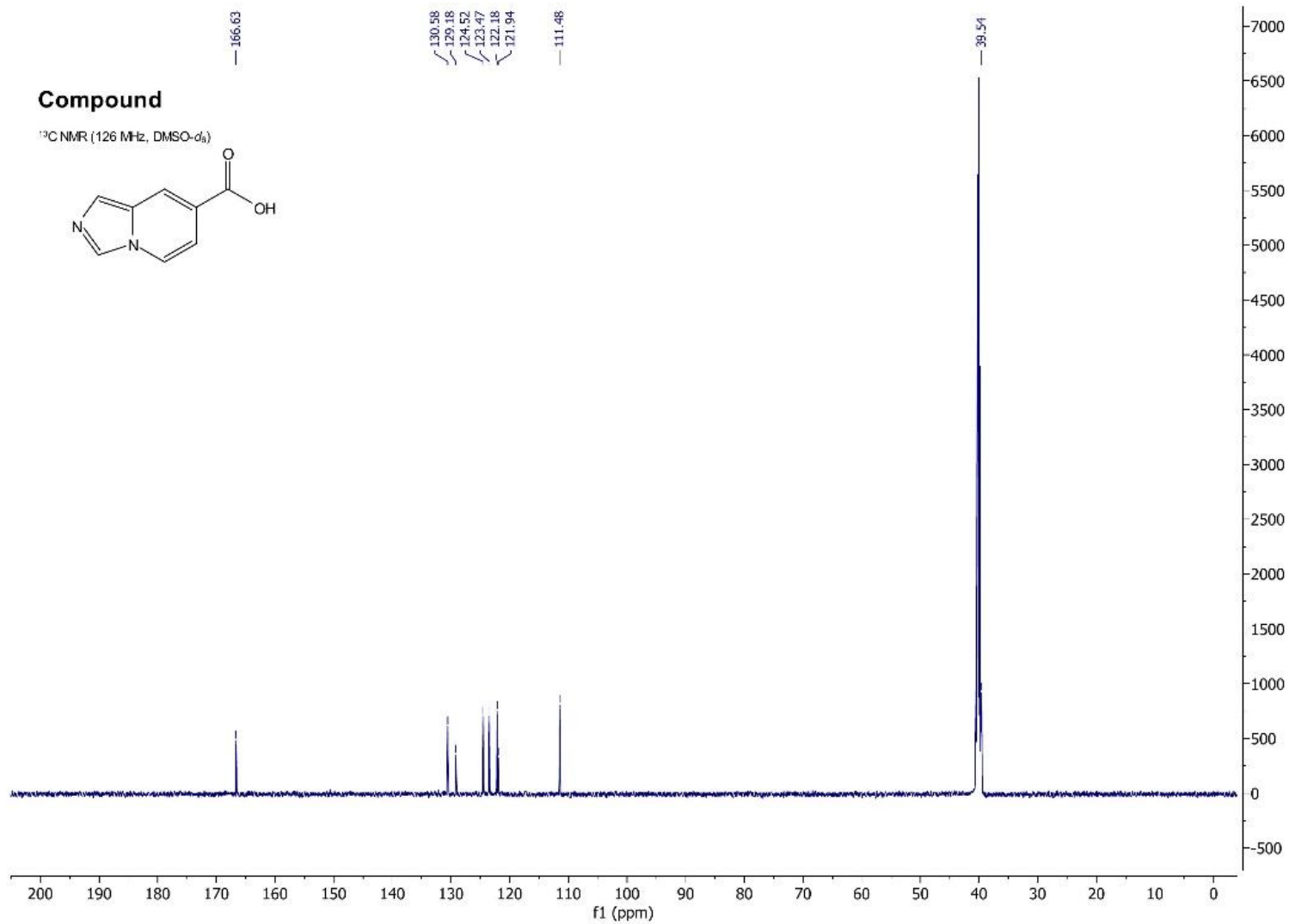
Impy-7-CO<sub>2</sub>H



Imidazo[1,5-a]pyridine-7-carboxylic acid, orange powder, M.p. above 236°C, yield 56%.



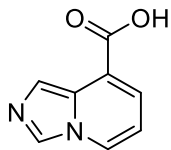
<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 13.04 (br.s, 1H), 8.55 (s, 1H), 8.35 (d, *J* = 7.3 Hz, 1H), 8.25 (s, 1H), 7.68 (s, 1H), 7.01 (dd, *J* = 7.4, 1.7 Hz, 1H).



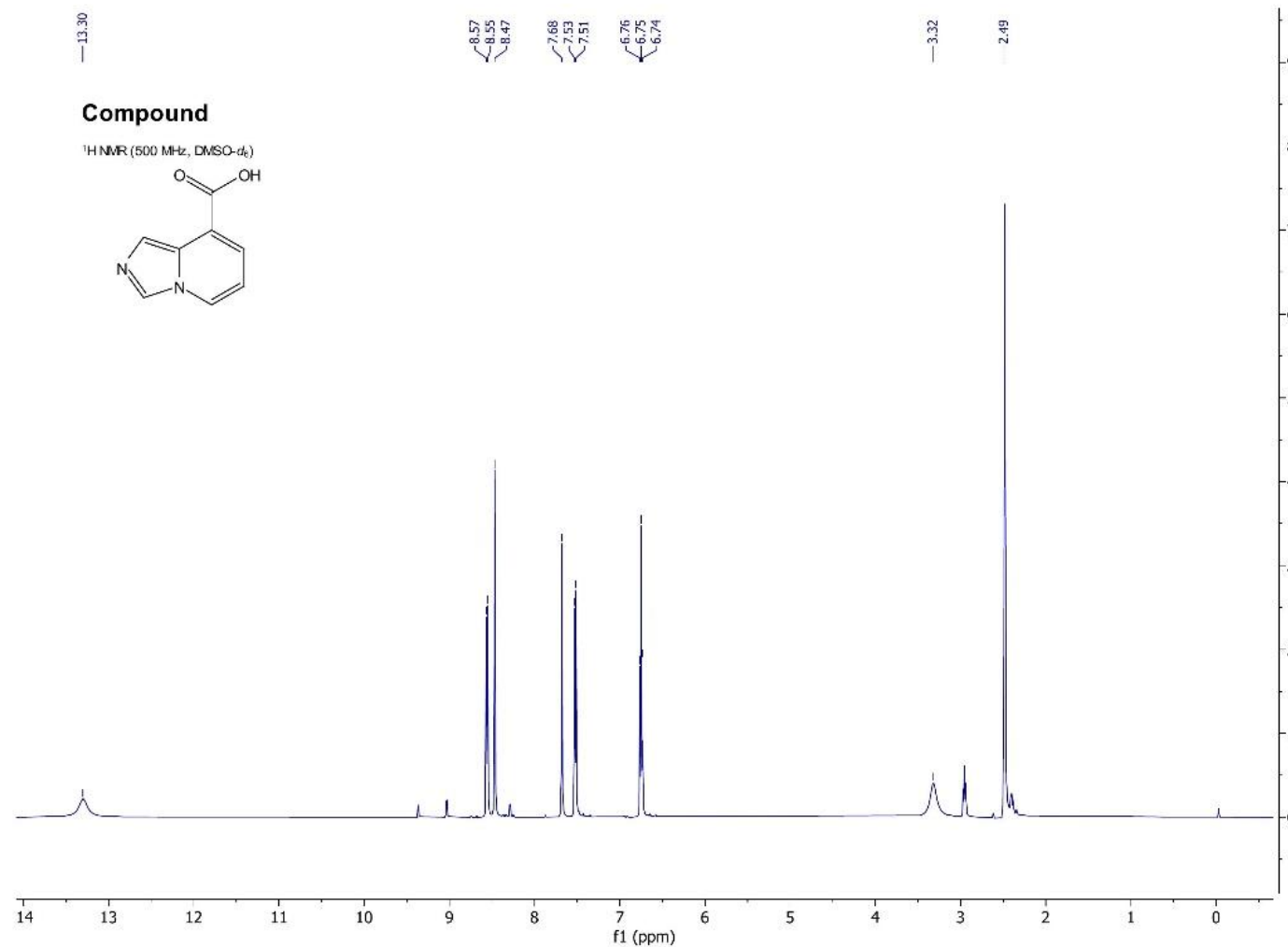
<sup>13</sup>C NMR (126 MHz, DMSO) δ 166.6, 130.6, 129.2, 124.5, 123.5, 122.2, 121.9, 111.5.

LCMS, positive mode, m/z: 163.0 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for **C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>** [M+H]<sup>+</sup>: 162.0429; found: 162.0429.

Impy-8-CO<sub>2</sub>H



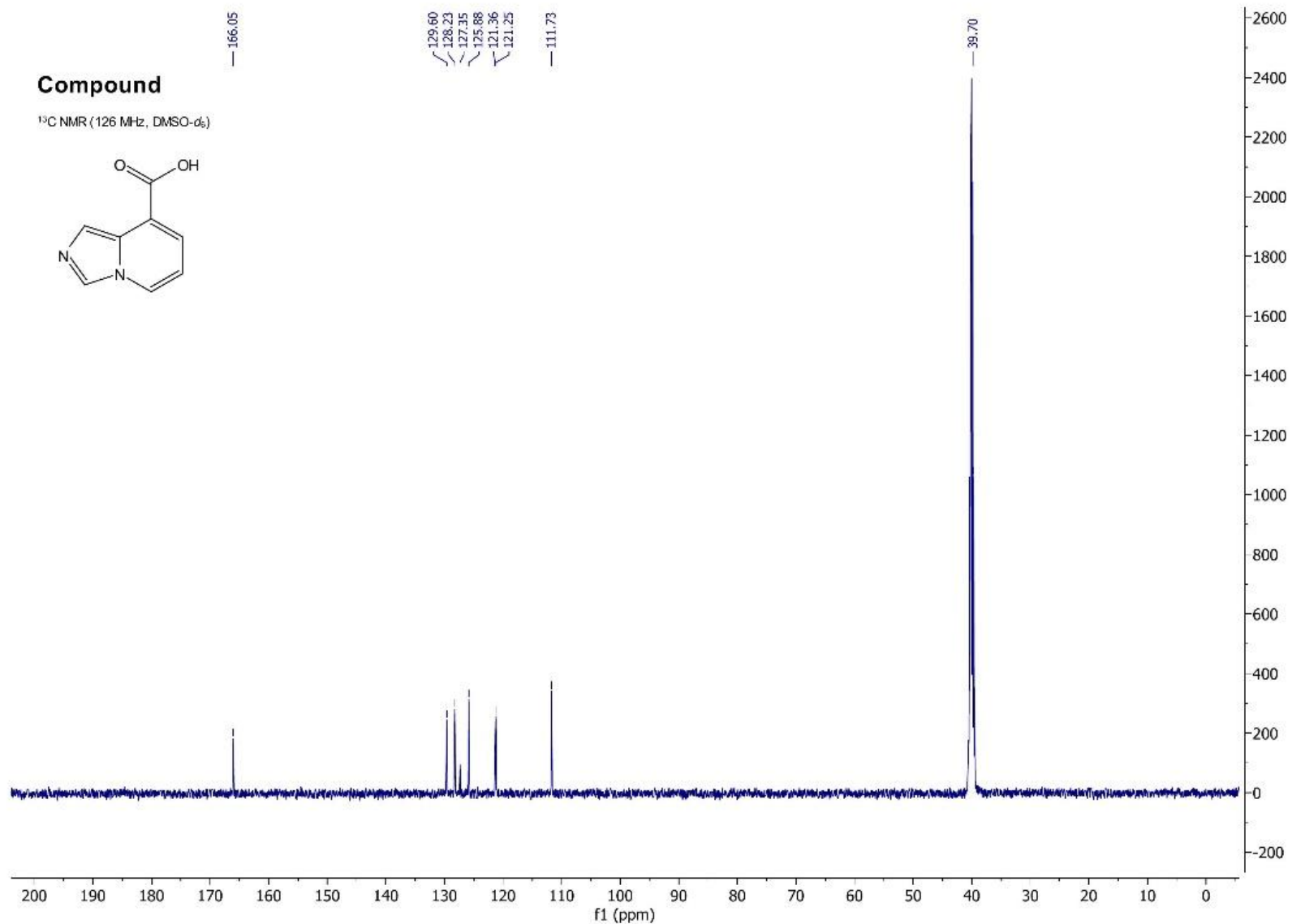
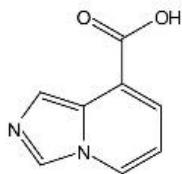
Imidazo[1,5-a]pyridine-8-carboxylic acid, light-green powder, M.p. above 246 °C, yield 42%.



<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 13.30 (br.s, 1H), 8.56 (d, *J* = 7.0 Hz, 1H), 8.47 (s, 1H), 7.68 (s, 1H), 7.52 (d, *J* = 6.8 Hz, 1H), 6.75 (t, *J* = 6.8 Hz, 1H).

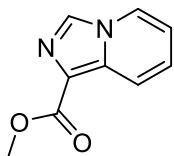
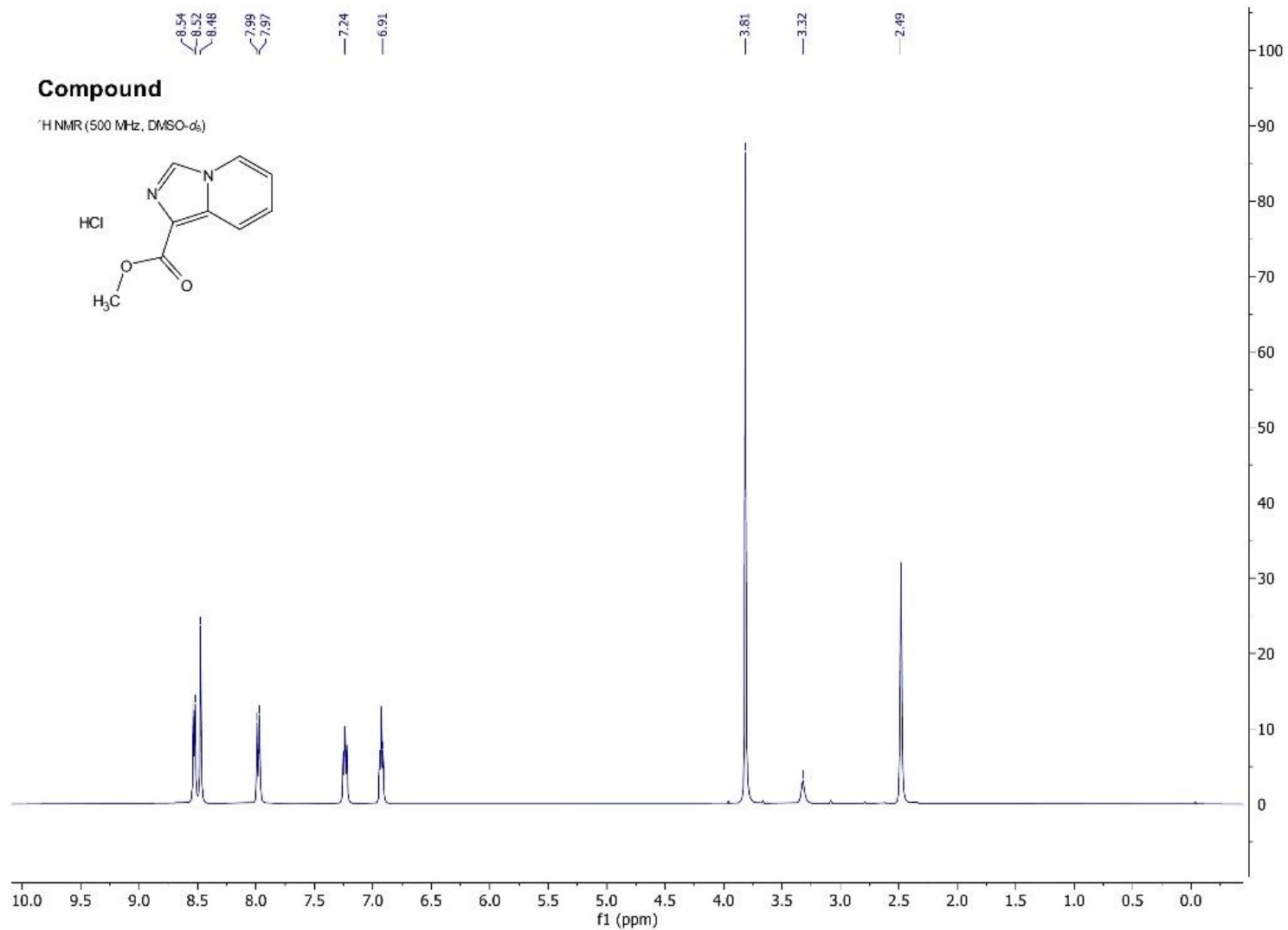
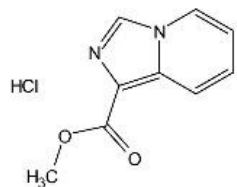
**Compound**

<sup>13</sup>C NMR (126 MHz, DMSO-d<sub>6</sub>)



<sup>13</sup>C NMR (126 MHz, DMSO)  $\delta$  166.1, 129.6, 128.2, 127.3, 125.9, 121.4, 121.2, 111.7.

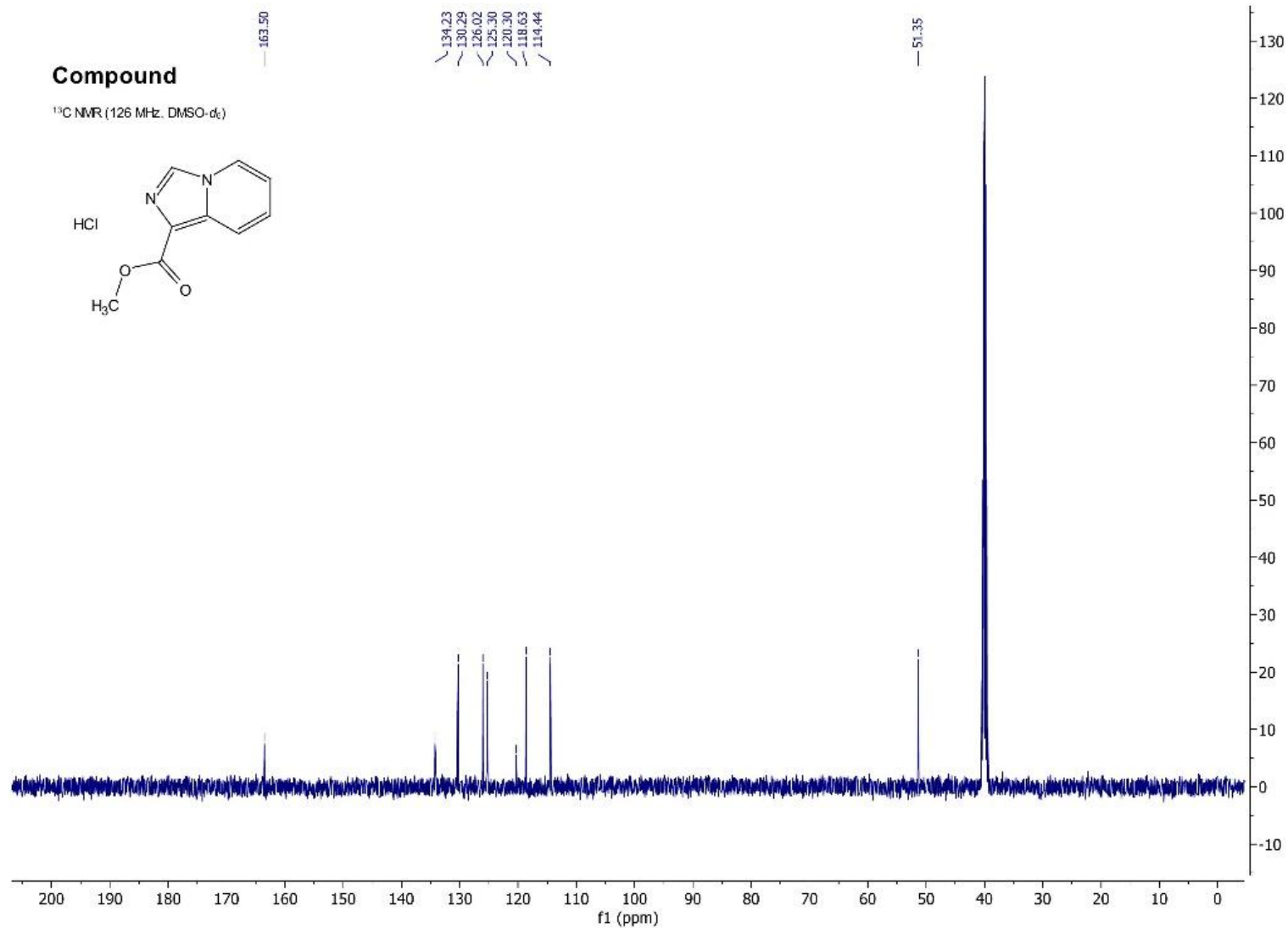
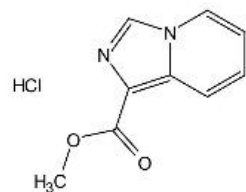
LCMS, positive mode, m/z: 163.0 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 162.0429; found: 162.0427.

**Impy-1-CO<sub>2</sub>Me****Methyl imidazo[1,5-a]pyridine-1-carboxylate, light-yellow powder, M.p. 127-138 °C, yield 58%.****Compound**<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.53 (d, *J* = 6.9 Hz, 1H), 8.47 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.24 (dd, *J* = 9.2, 6.5 Hz, 1H), 6.93 (t, *J* = 6.7 Hz, 1H), 3.81 (s, 3H).

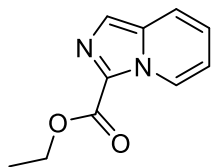
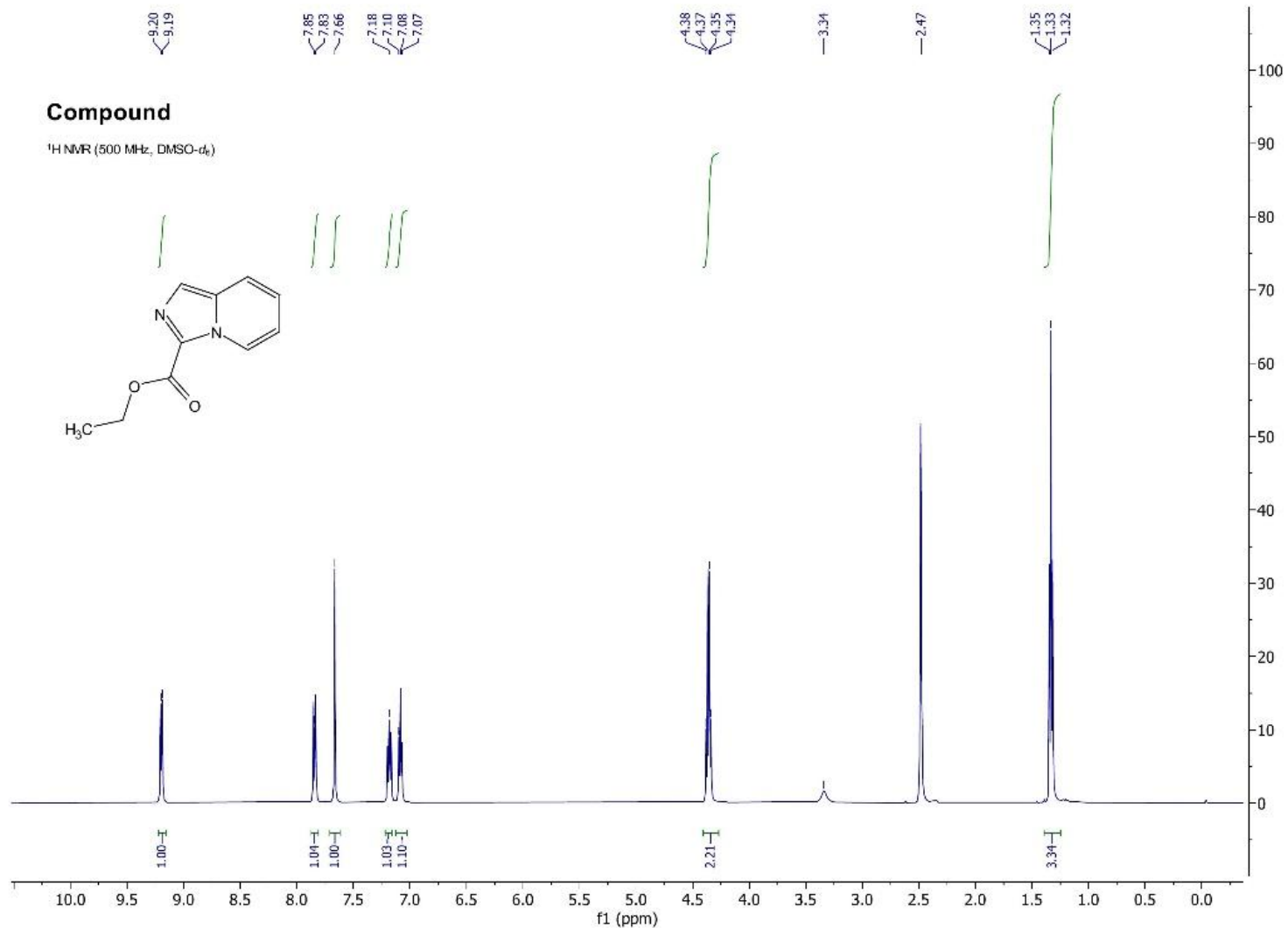
**Compound**

<sup>13</sup>C NMR (126 MHz, DMSO-d<sub>6</sub>)



<sup>13</sup>C NMR (126 MHz, dmsO)  $\delta$  163.5, 134.2, 130.3, 126.0, 125.3, 120.3, 118.6, 114.4, 51.4.

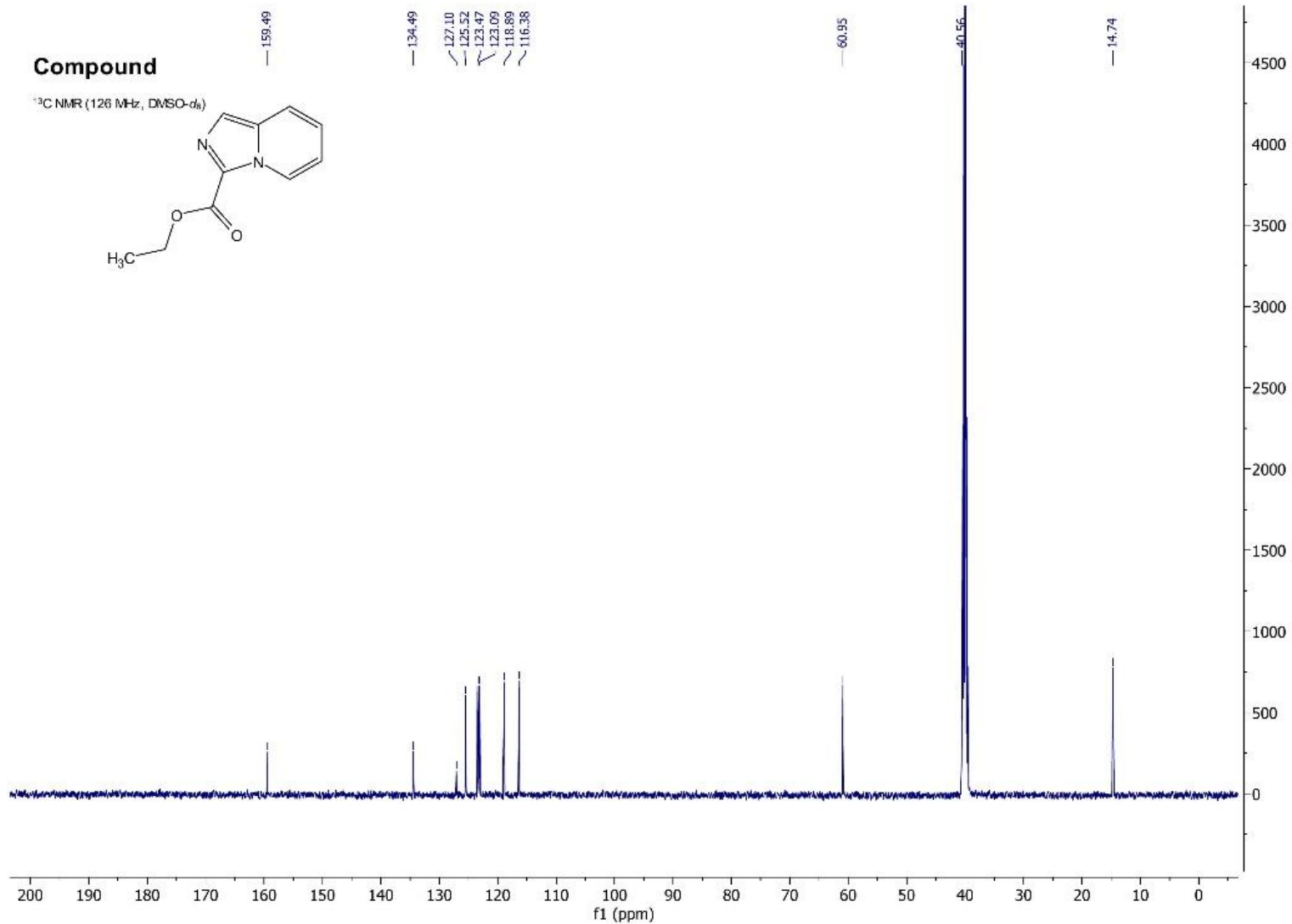
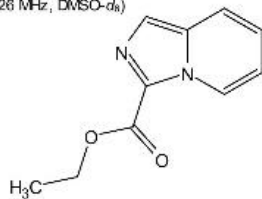
LCMS, positive mode, m/z: 177.0 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 176.0585; found: 176.0583.

**Impy-3-CO<sub>2</sub>Et****Ethyl imidazo[1,5-a]pyridine-3-carboxylate, grey crystals, M.p. non-informative, yield 91%.**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.20 (d, *J* = 7.3 Hz, 1H), 7.84 (d, *J* = 9.3 Hz, 1H), 7.66 (s, 1H), 7.18 (m, 1H), 7.08 (td, *J* = 6.9, 1.3 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

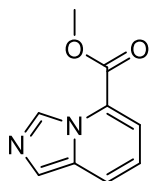
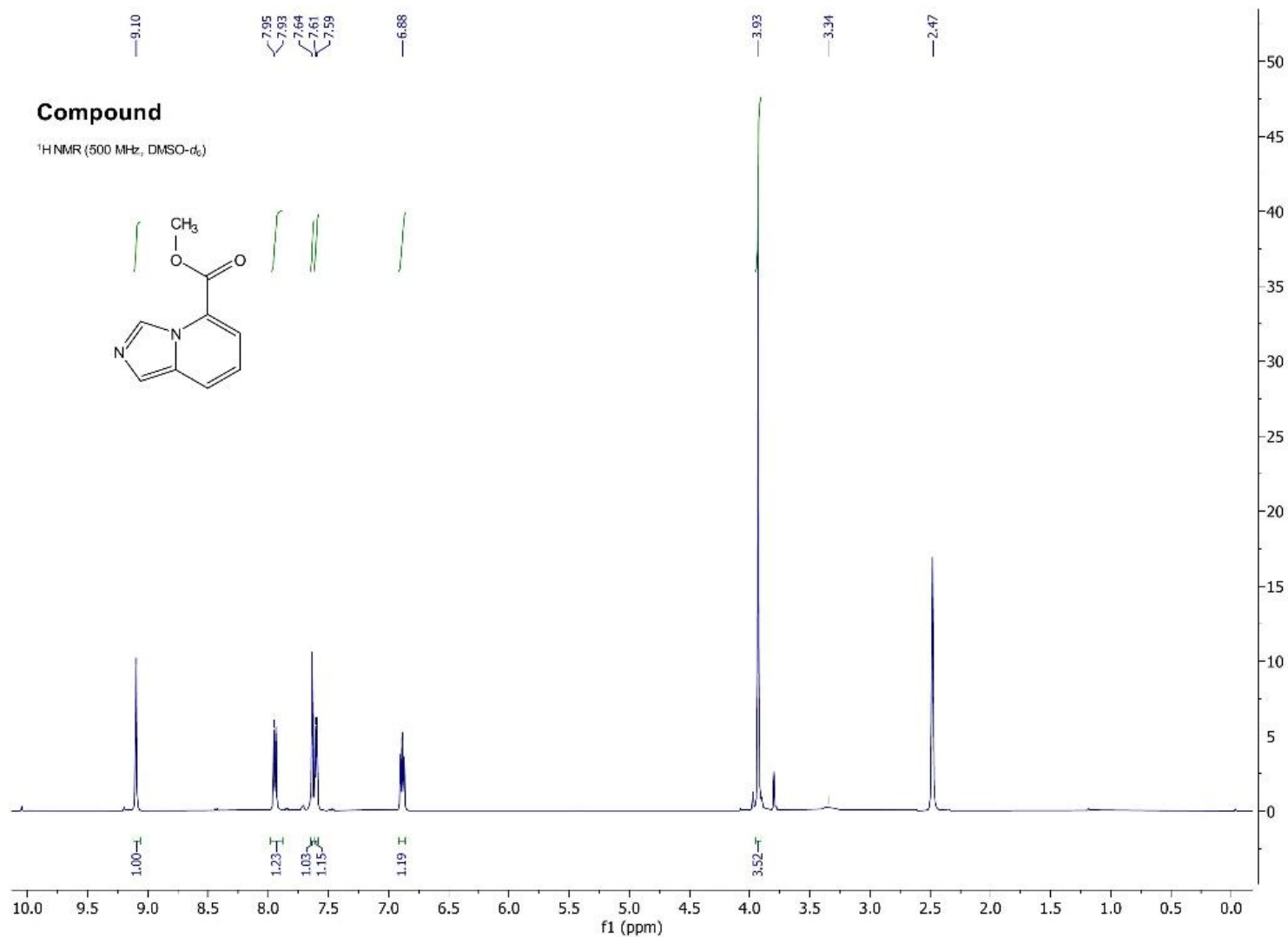
**Compound**

<sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>)



<sup>13</sup>C NMR (126 MHz, DMSO)  $\delta$  159.5, 134.5, 127.1, 125.5, 123.5, 123.1, 118.9, 116.4, 61.0, 14.7.

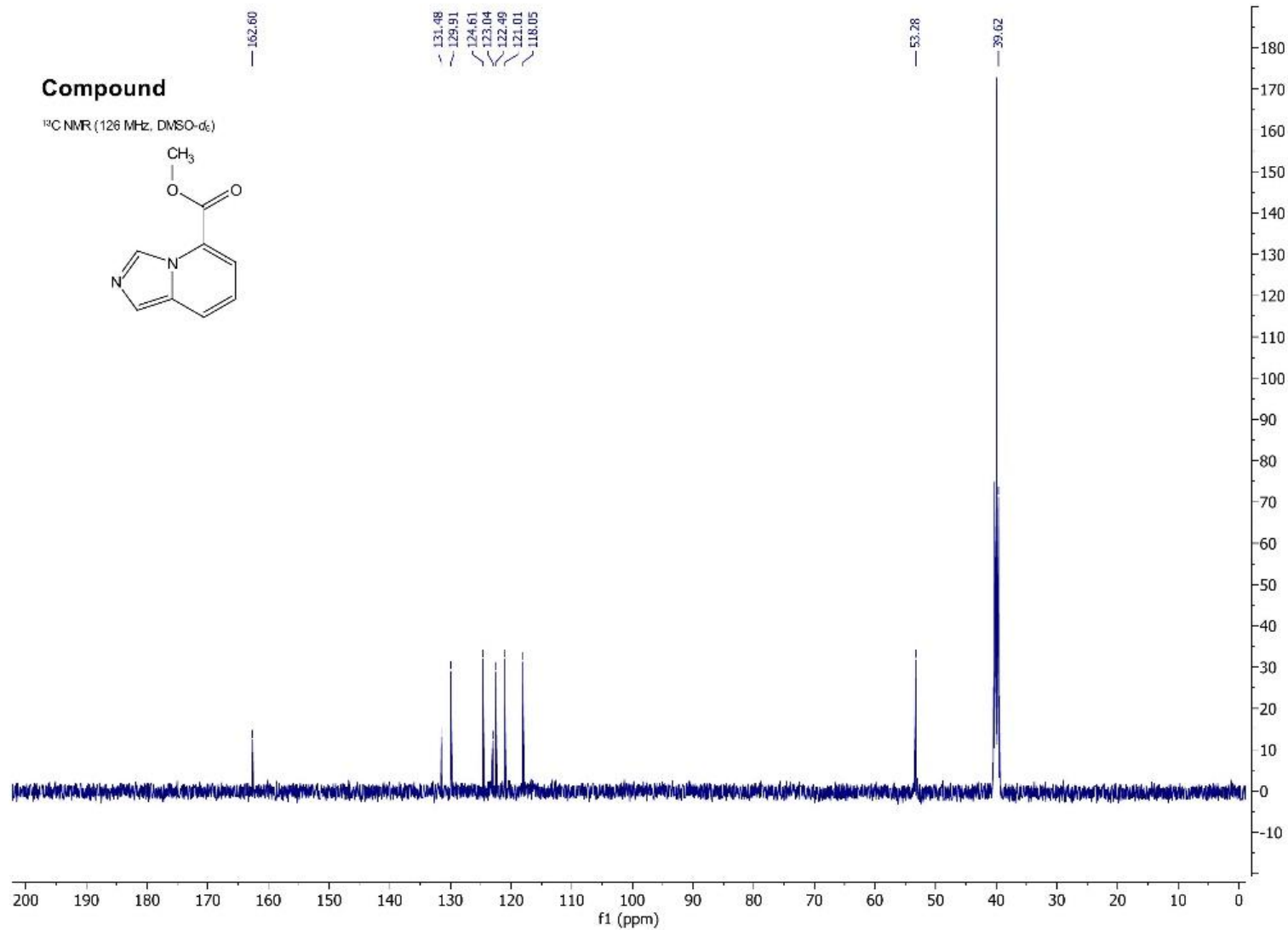
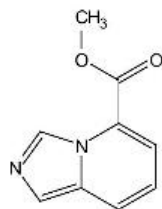
LCMS, positive mode,  $m/z$ : 191.2 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 190.0742; found: 190.0737.

**Impy-5-CO<sub>2</sub>Me****Methyl imidazo[1,5-a]pyridine-5-carboxylate, yellow crystal powder, M.p. 121 °C, yield 48%.**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.10 (s, 1H), 7.94 (d, *J* = 8.9 Hz, 1H), 7.63 (s, 1H), 7.60 (dd, *J* = 6.9, 1.2 Hz, 1H), 6.89 (td, *J* = 7.8, 1.9 Hz, 1H), 3.93 (s, 3H).

**Compound**

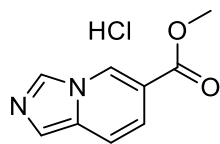
<sup>13</sup>C NMR (126 MHz, DMSO-d<sub>6</sub>)



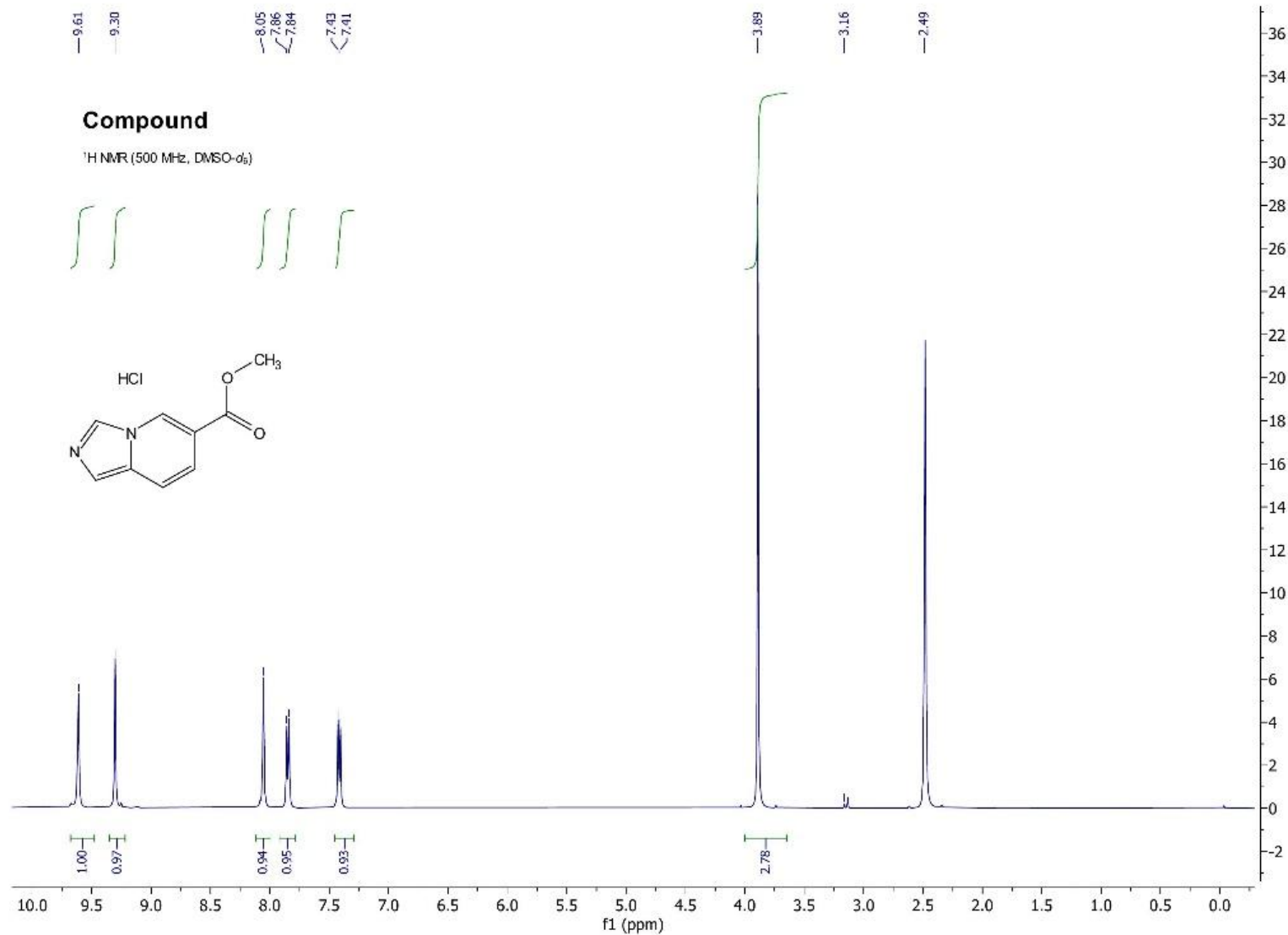
<sup>13</sup>C NMR (126 MHz, dmso)  $\delta$  162.6, 131.5, 129.9, 124.6, 123.0, 122.5, 121.0, 118.0, 53.3.

LCMS, positive mode, m/z: 177.0 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 176.0585; found: 176.0590.

Impy-6-CO<sub>2</sub>Me·HCl



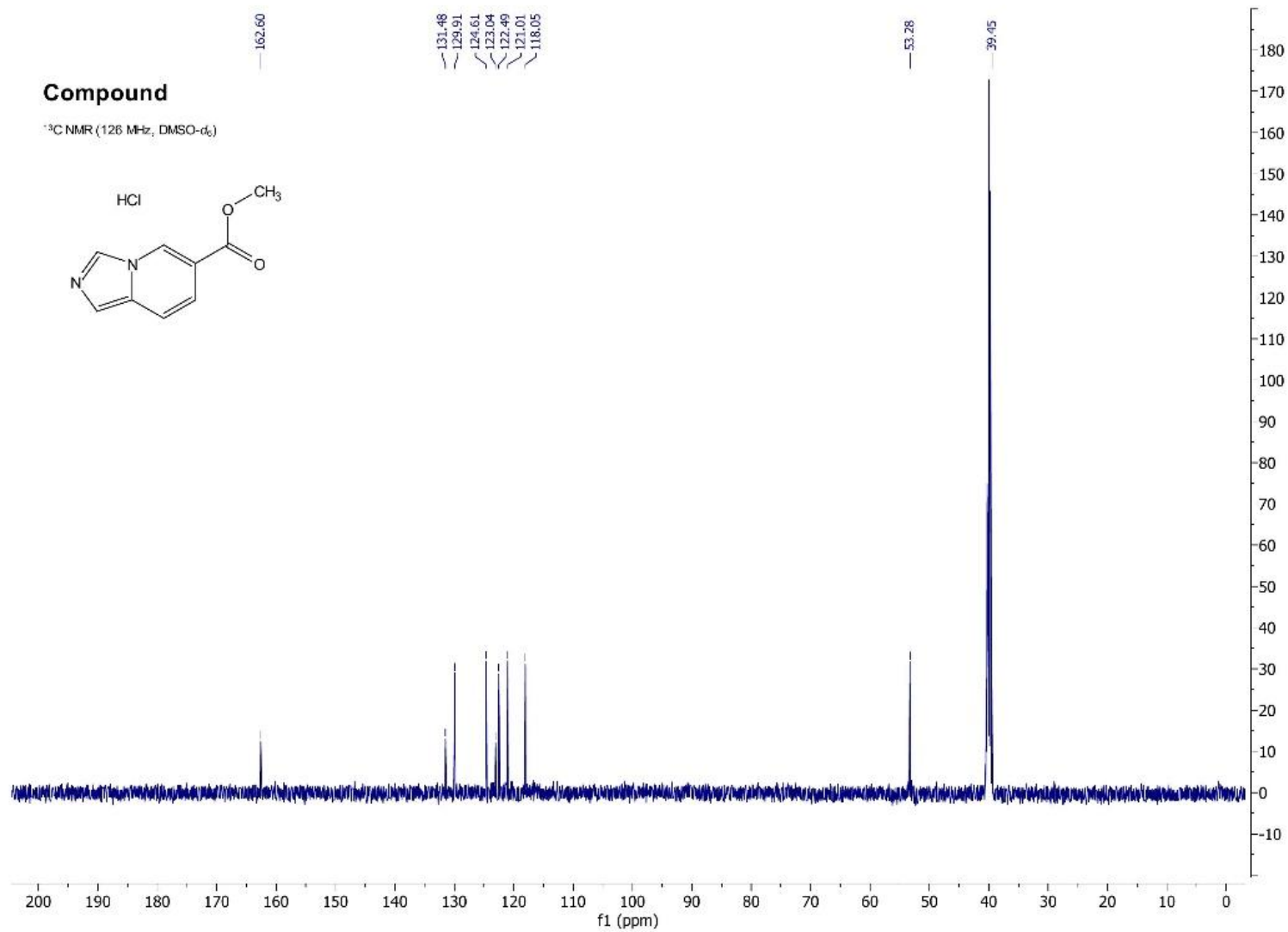
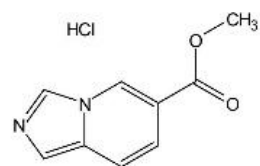
Methyl imidazo[1,5-a]pyridine-6-carboxylate hydrochloride, brown powder, yield 93 %, M.p. 173-197 °C.



<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.61 (s, 1H), 8.05 (s, 1H), 7.85 (d, *J* = 9.6 Hz, 1H), 7.42 (d, *J* = 9.7 Hz, 1H), 3.89 (s, 3H).

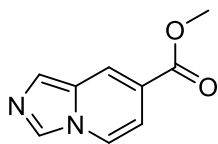
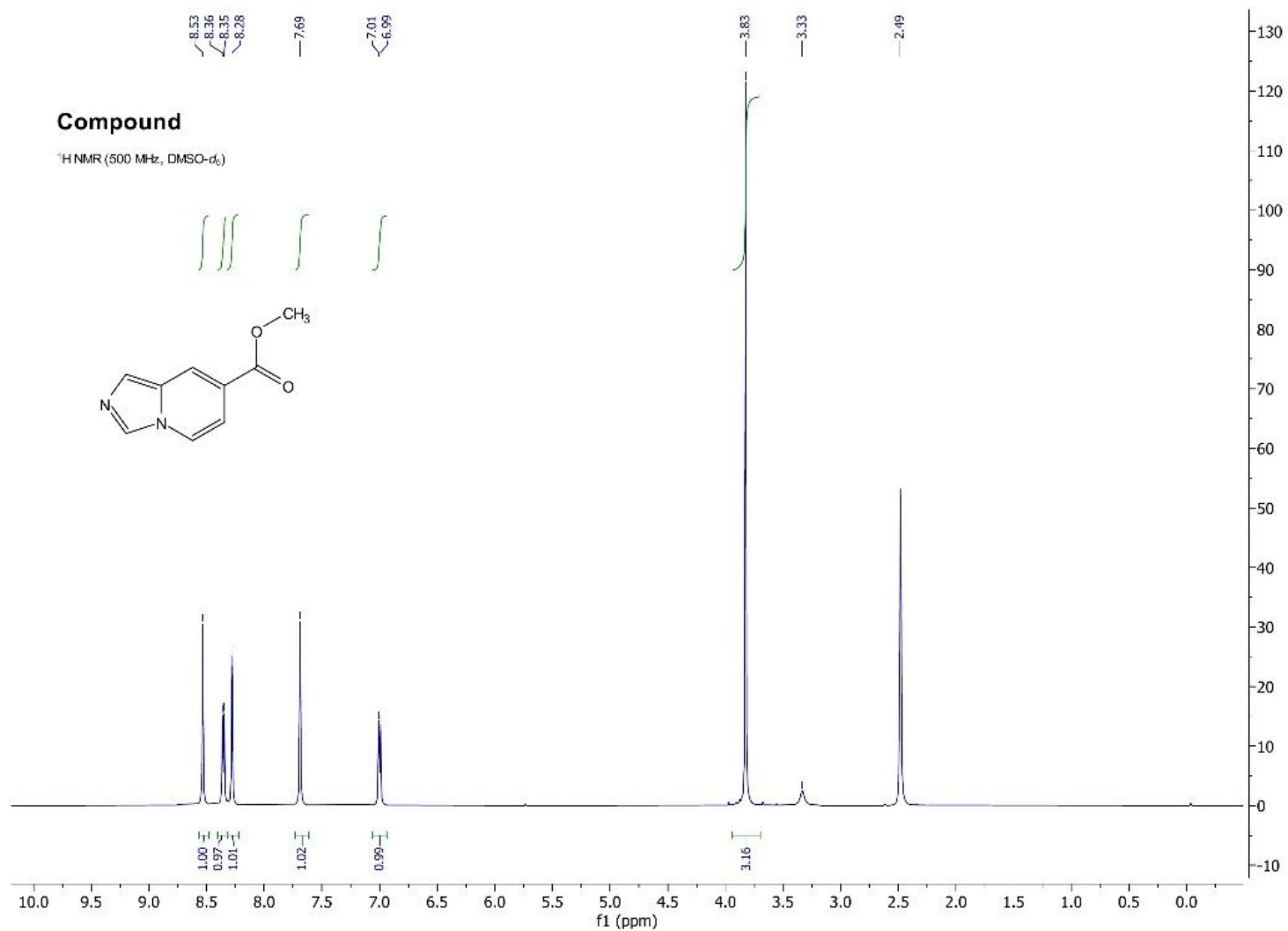
### Compound

<sup>13</sup>C NMR (126 MHz, DMSO-d<sub>6</sub>)

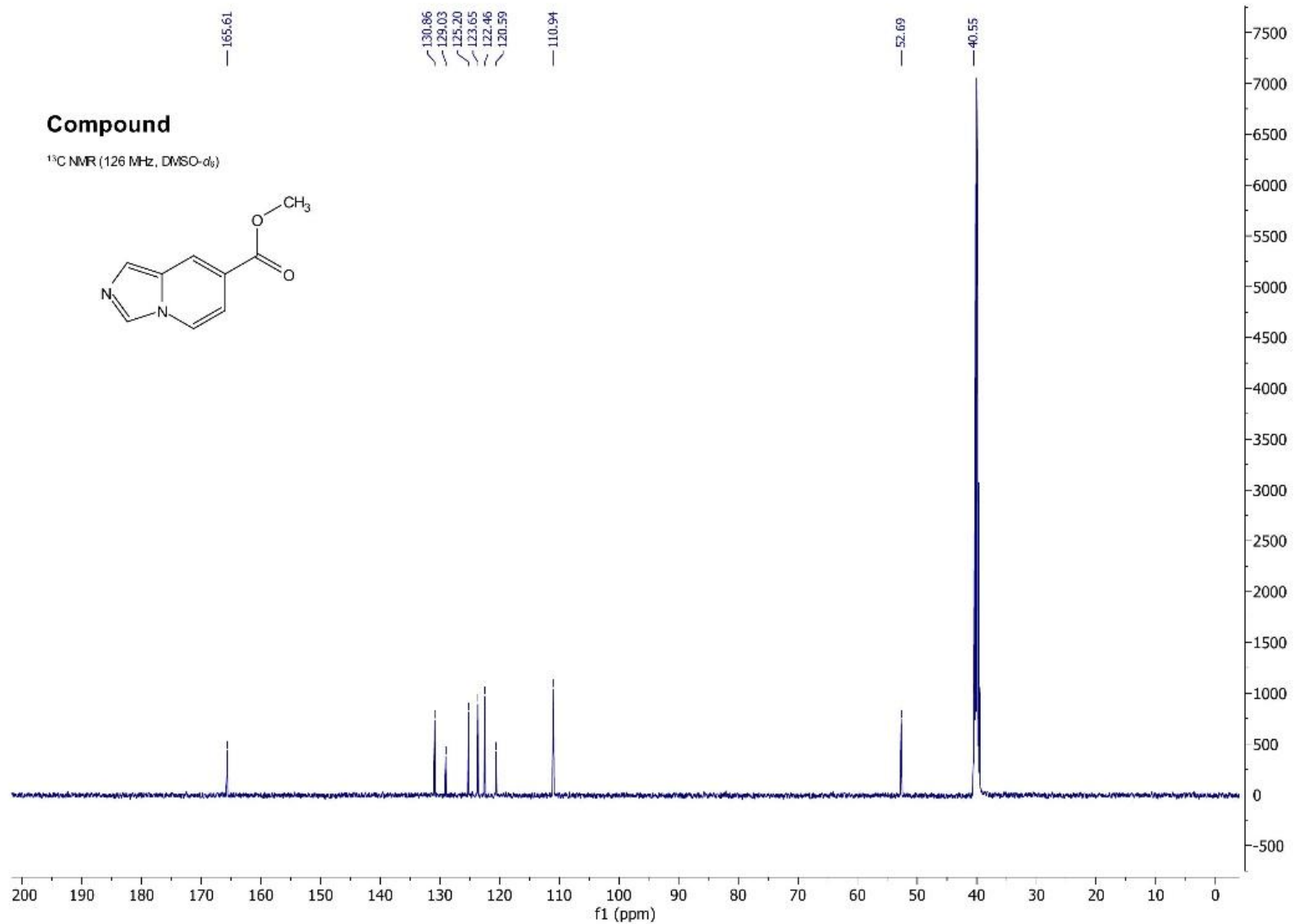


<sup>13</sup>C NMR (126 MHz, DMSO)  $\delta$  164.6, 129.7, 129.6, 128.9, 121.6, 119.5, 119.2, 113.6, 53.3.

LCMS, positive mode,  $m/z$ : 177.2 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>9</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 176.0585; found: 176.0586.

**Impy-7-CO<sub>2</sub>Me****Methyl imidazo[1,5-a]pyridine-7-carboxylate**, brown powder, yield 89%, M.p. 101 °C.

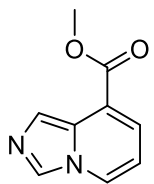
<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.53 (s, 1H), 8.36 (d, *J* = 7.4 Hz, 1H), 8.28 (s, 1H), 7.69 (s, 1H), 7.00 (dd, *J* = 7.3, 1.7 Hz, 1H), 3.83 (s, 3H).



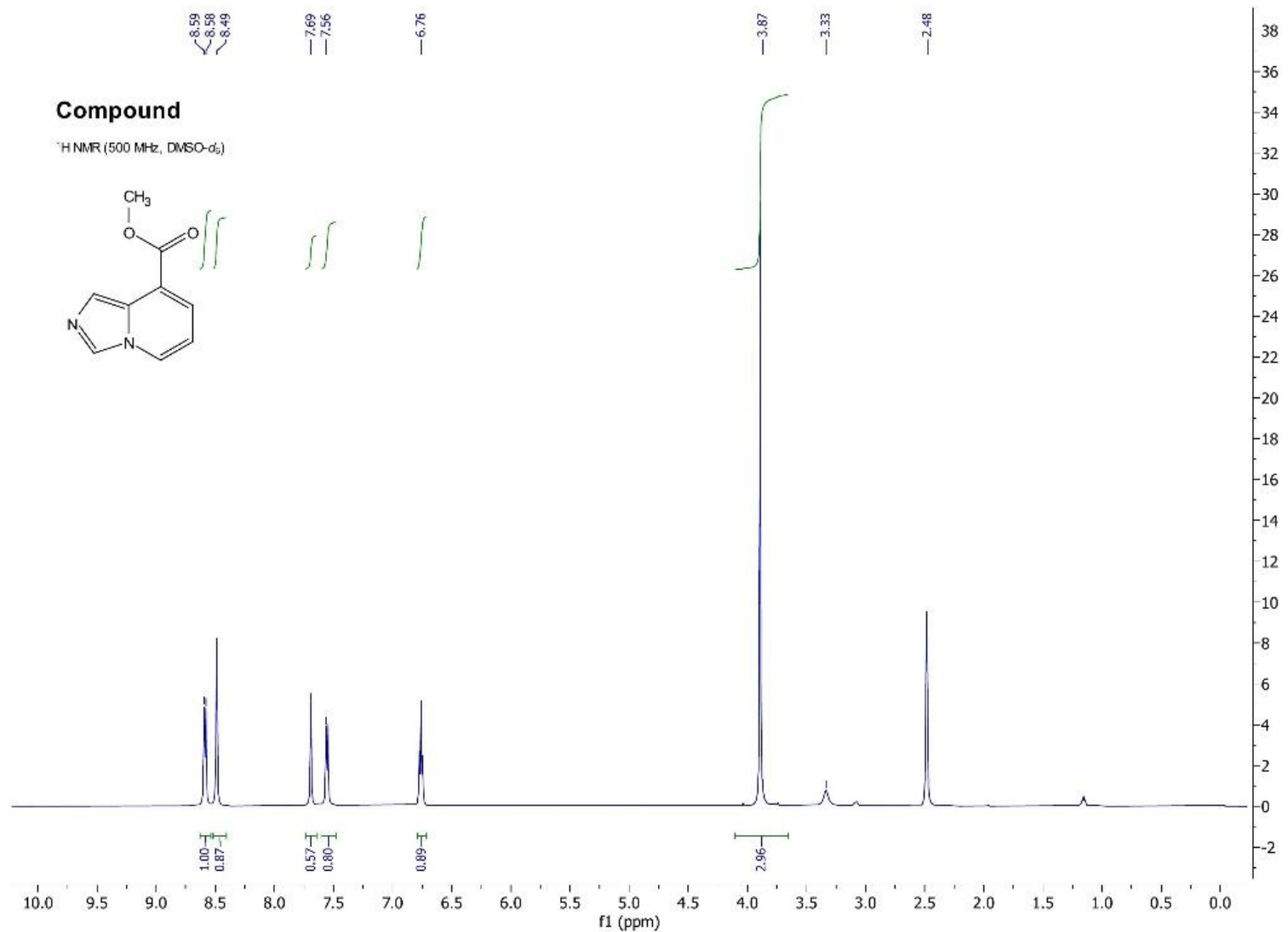
<sup>13</sup>C NMR (126 MHz, DMSO) δ 165.6, 130.9, 129.0, 125.2, 123.6, 122.5, 120.6, 110.9, 52.7.

LCMS, positive mode, m/z: 177.2 [M+H]<sup>+</sup>. HRMS (ESI): calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 176.0585; found: 176.0586.

Impy-8-CO<sub>2</sub>Me



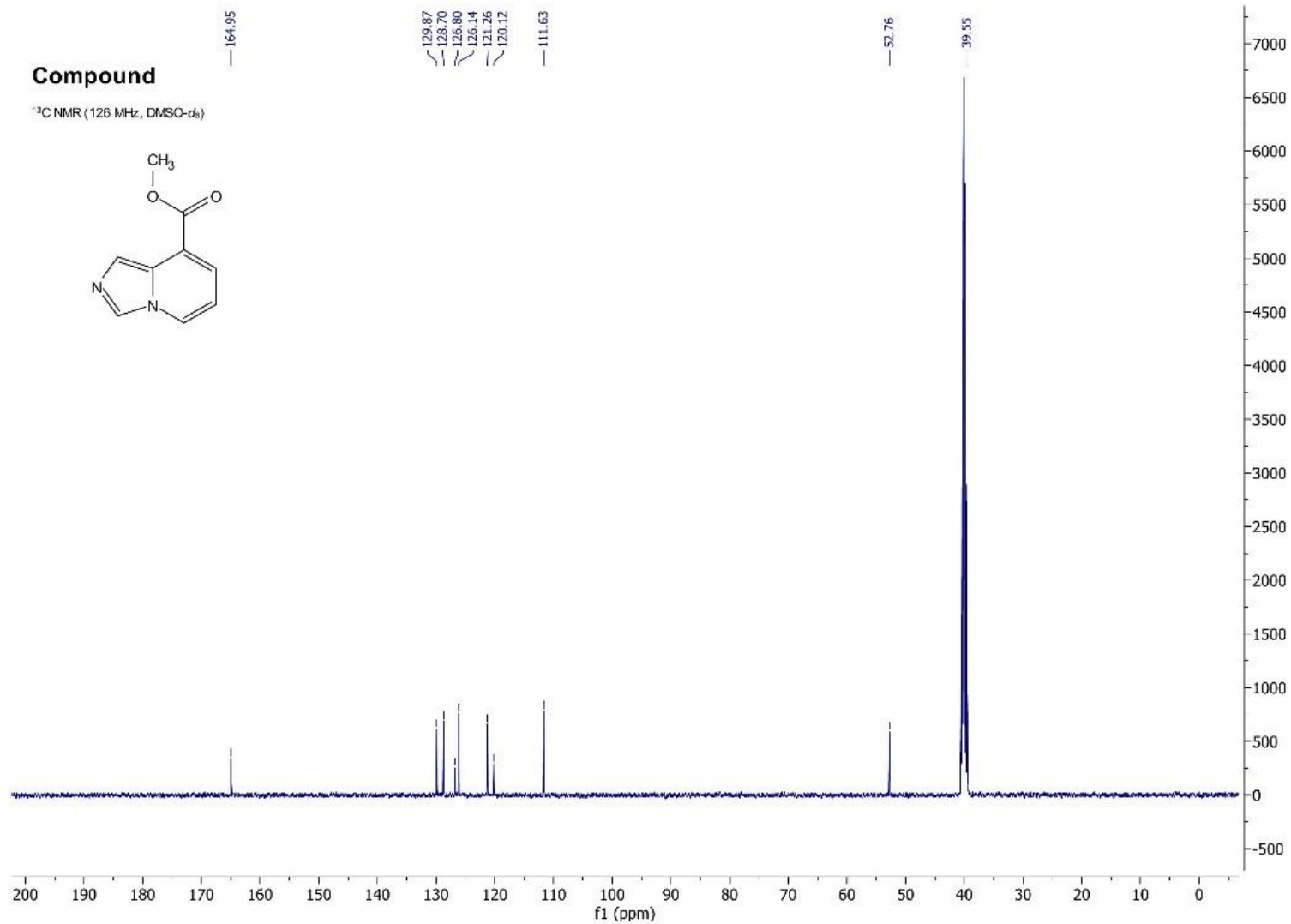
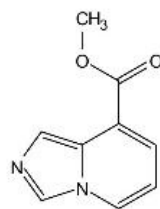
Methyl imidazo[1,5-a]pyridine-8-carboxylate, brown powder, yield 84%, M.p. 86 °C.



<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.59 (d, *J* = 6.9 Hz, 1H), 8.49 (s, 1H), 7.69 (s, 1H), 7.56 (d, *J* = 6.7 Hz, 1H), 6.76 (t, *J* = 6.8 Hz, 1H), 3.88 (m, 3H).

**Compound**

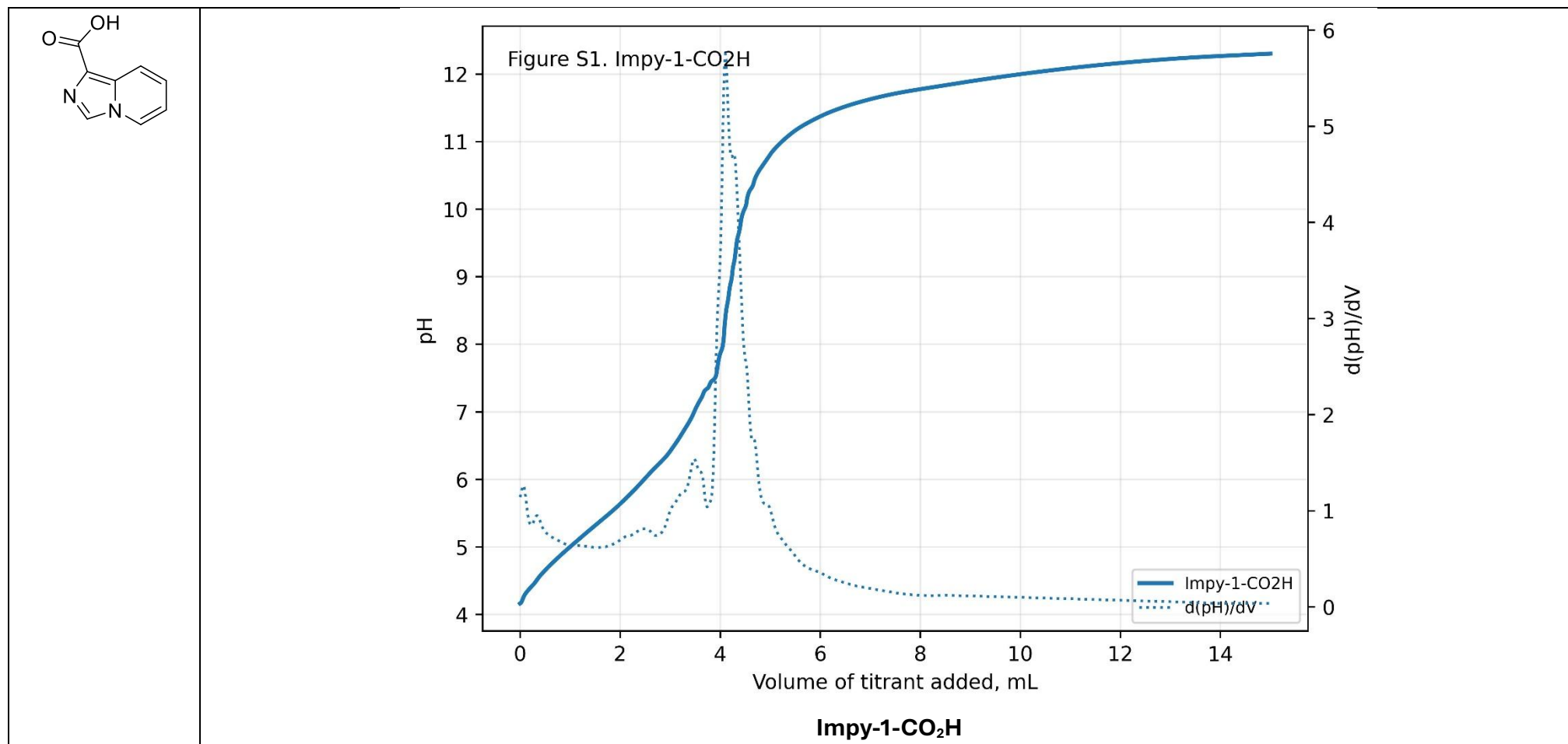
<sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>)

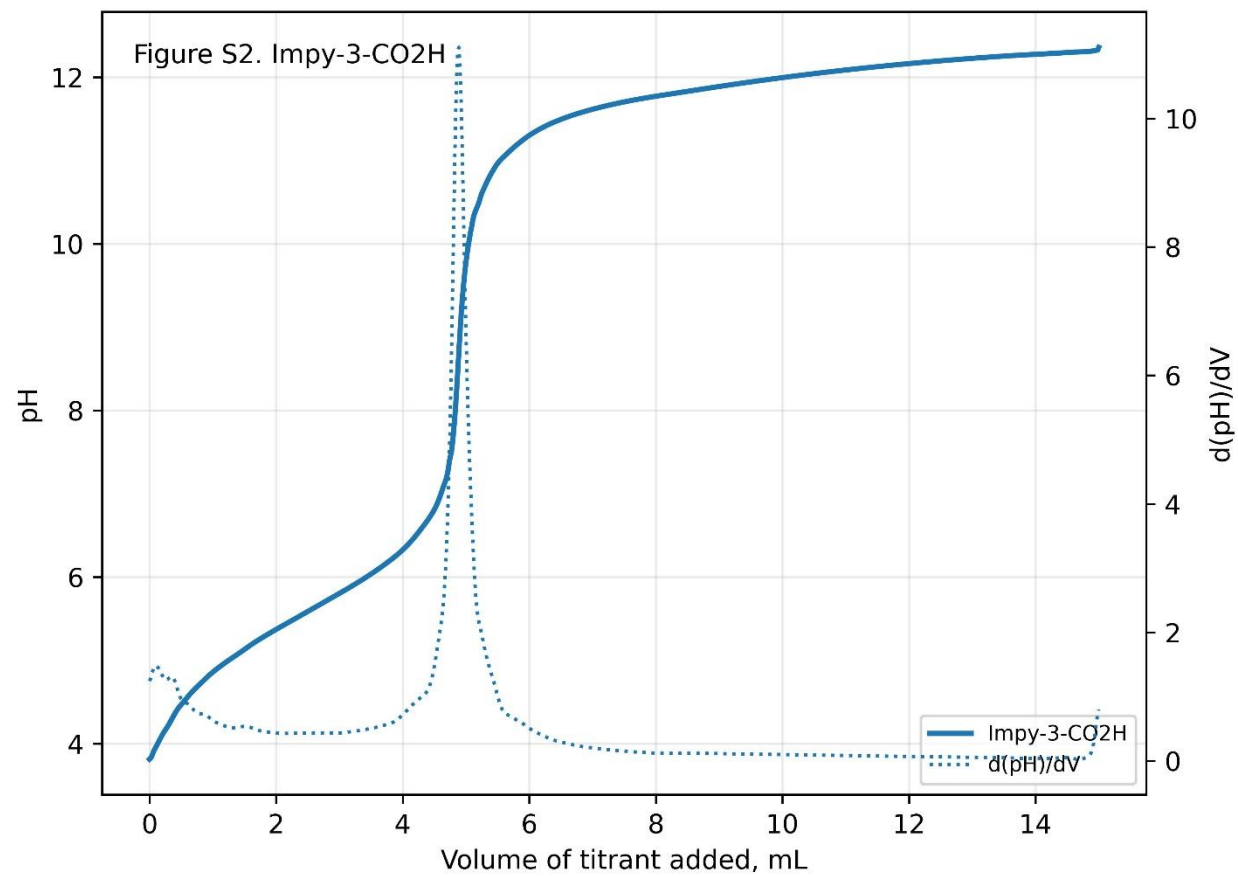


<sup>13</sup>C NMR (126 MHz, DMSO)  $\delta$  165.0, 129.9, 128.7, 126.8, 126.1, 121.3, 120.1, 111.6, 52.8.

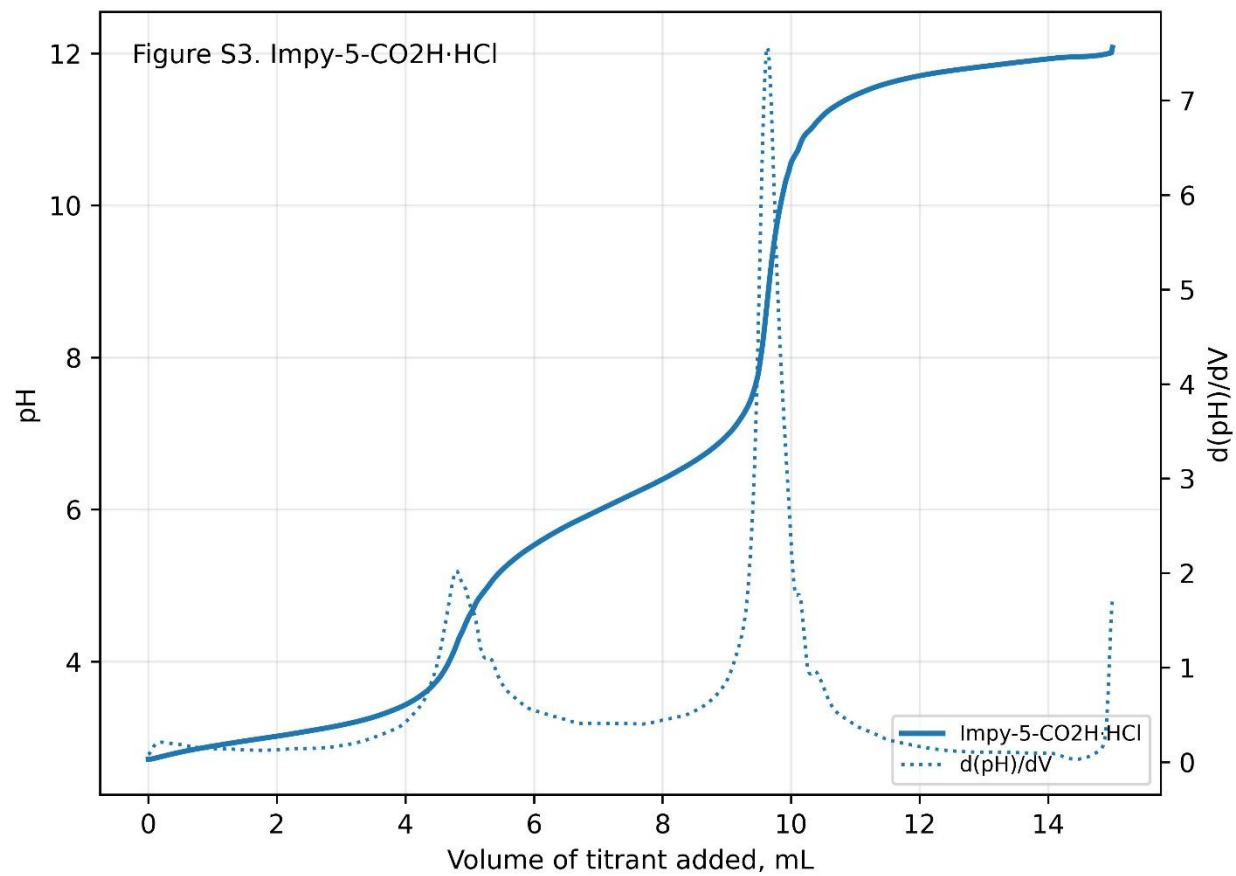
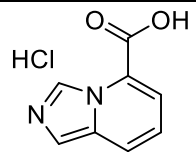
LCMS, positive mode,  $m/z$ : 177.0  $[M+H]^+$ . HRMS (ESI): calcd. for  $C_9H_8N_2O_2$   $[M+H]^+$ : 176.0585; found: 176.0586.

**Table S2.** Potentiometric titration of compounds

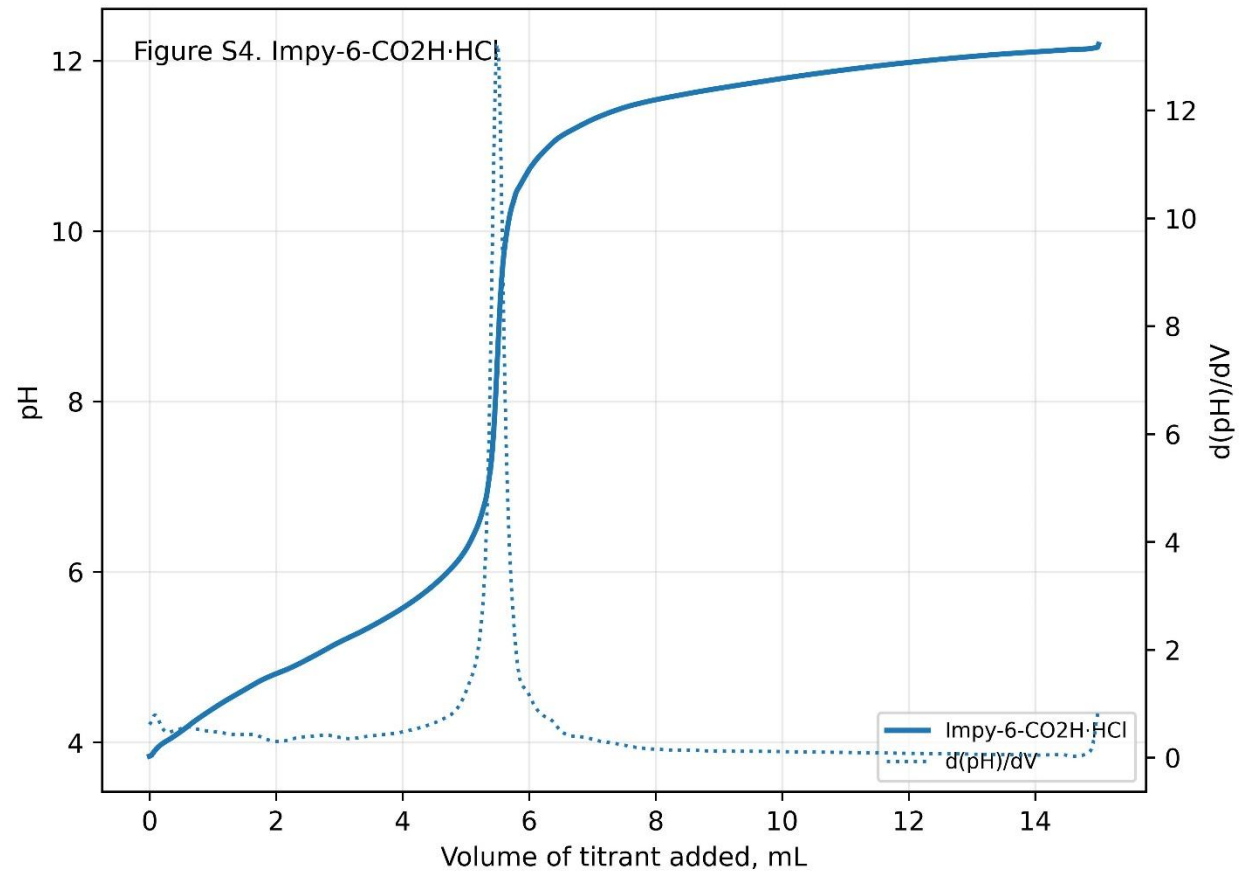
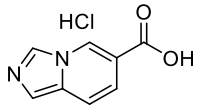




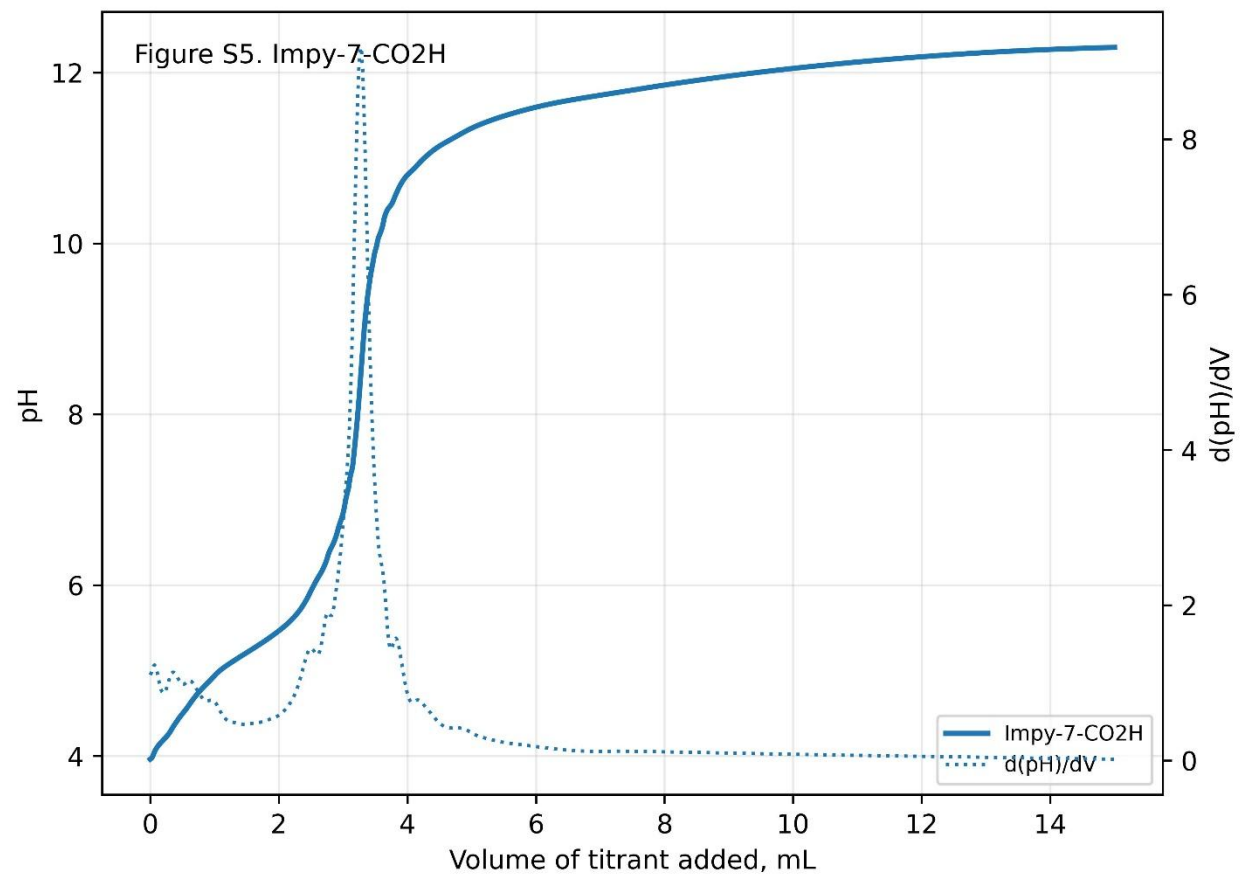
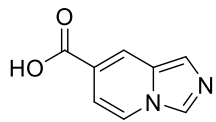
**Impy-3-CO<sub>2</sub>H**



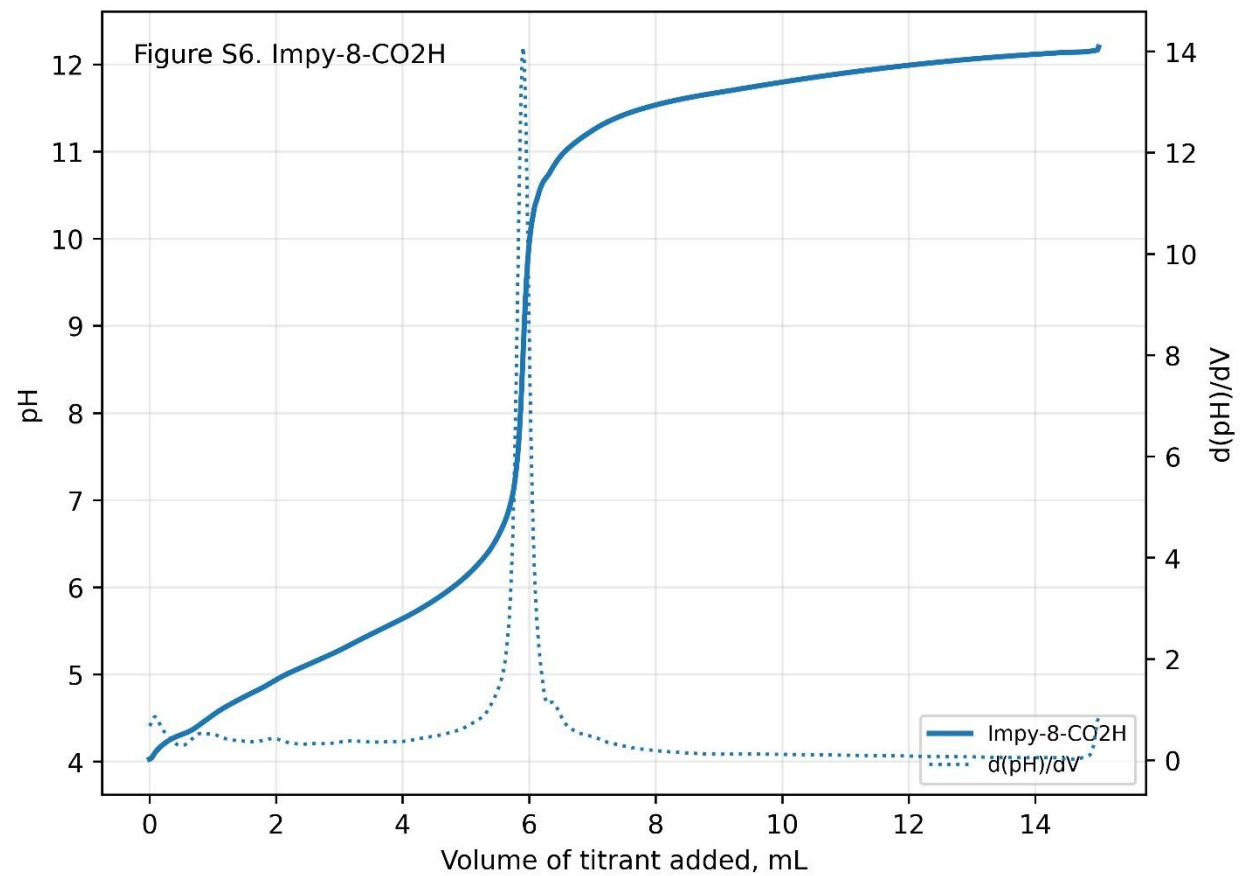
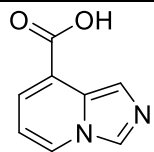
**Impy-5-CO<sub>2</sub>H·HCl**



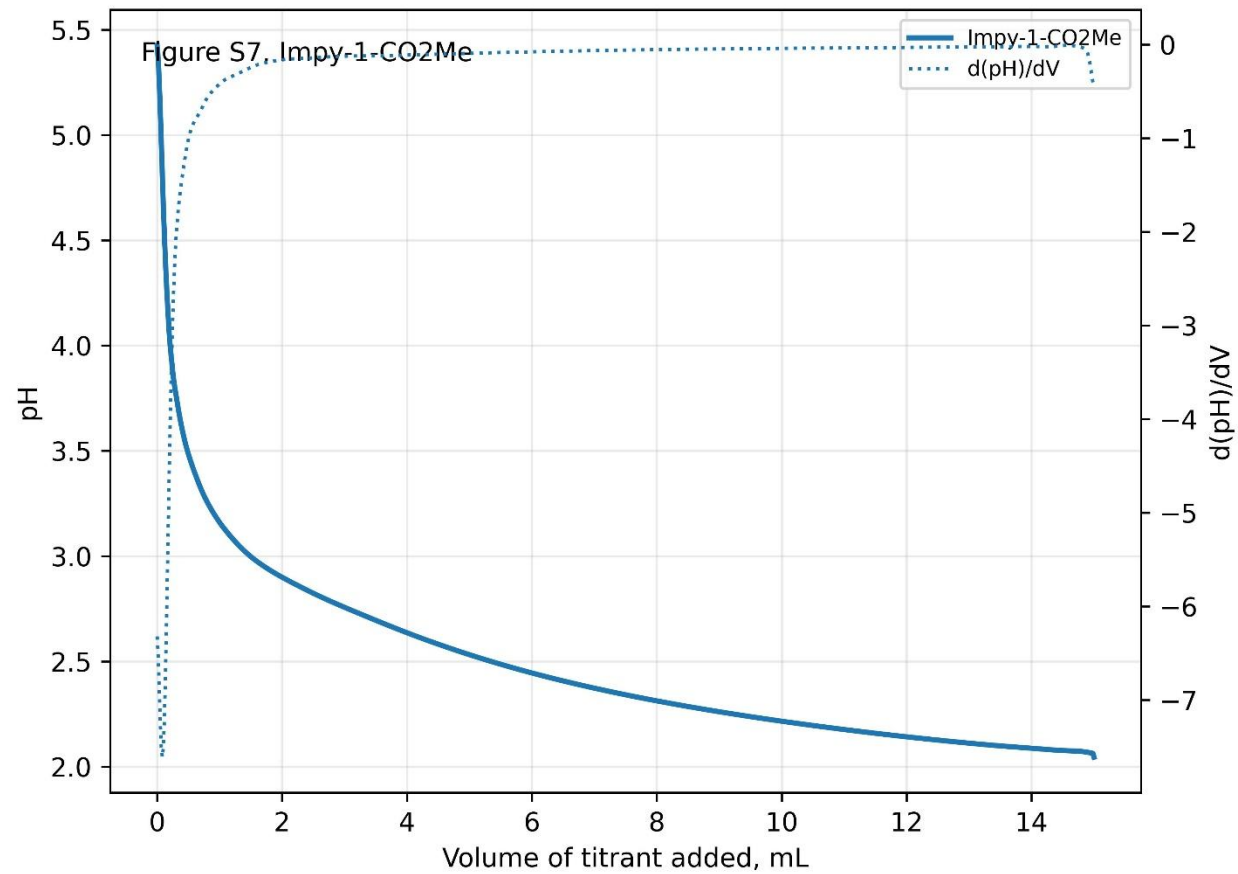
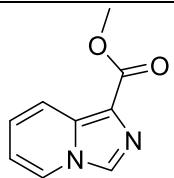
**Impy-6-CO<sub>2</sub>H·HCl**



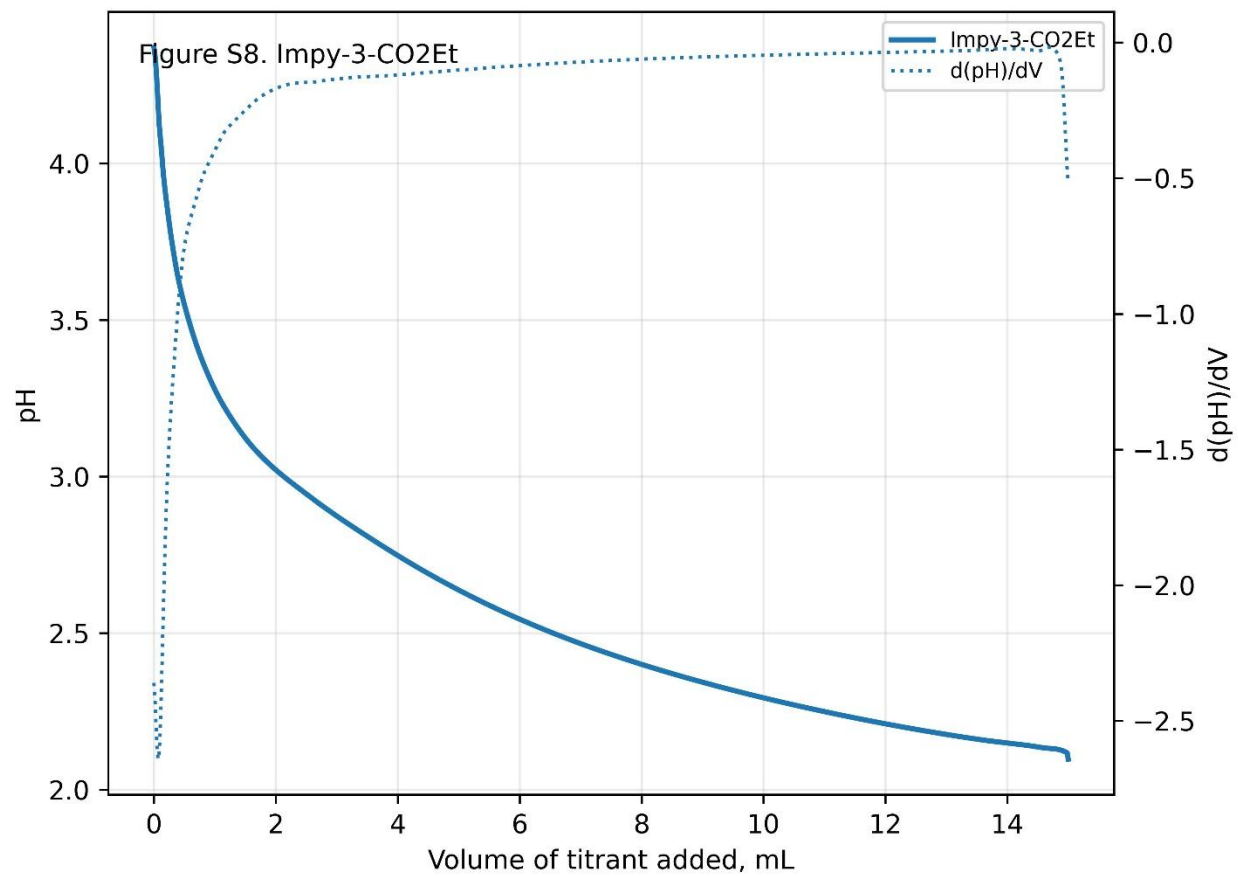
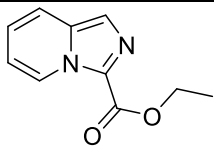
**Impy-7-CO<sub>2</sub>H**



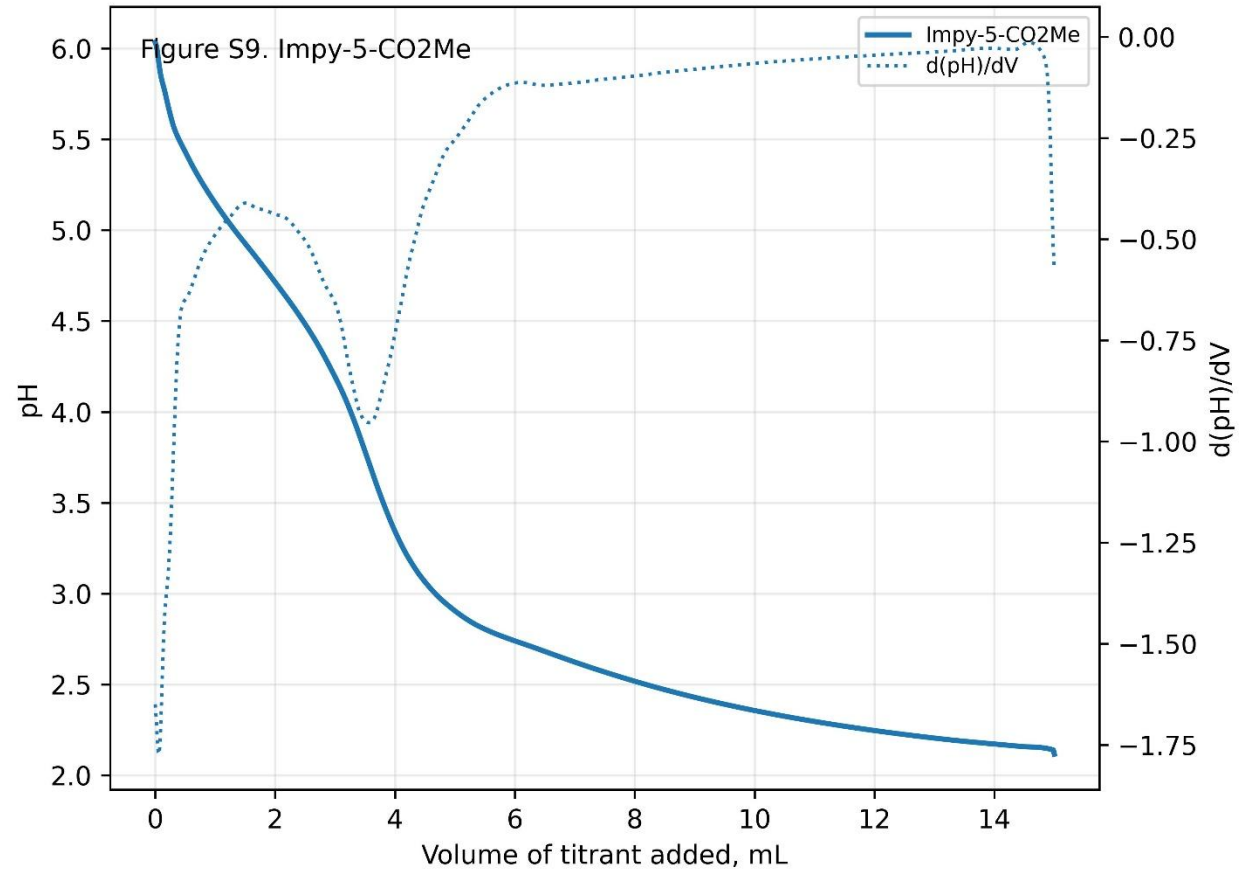
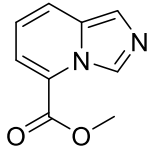
**Impy-8-CO<sub>2</sub>H**



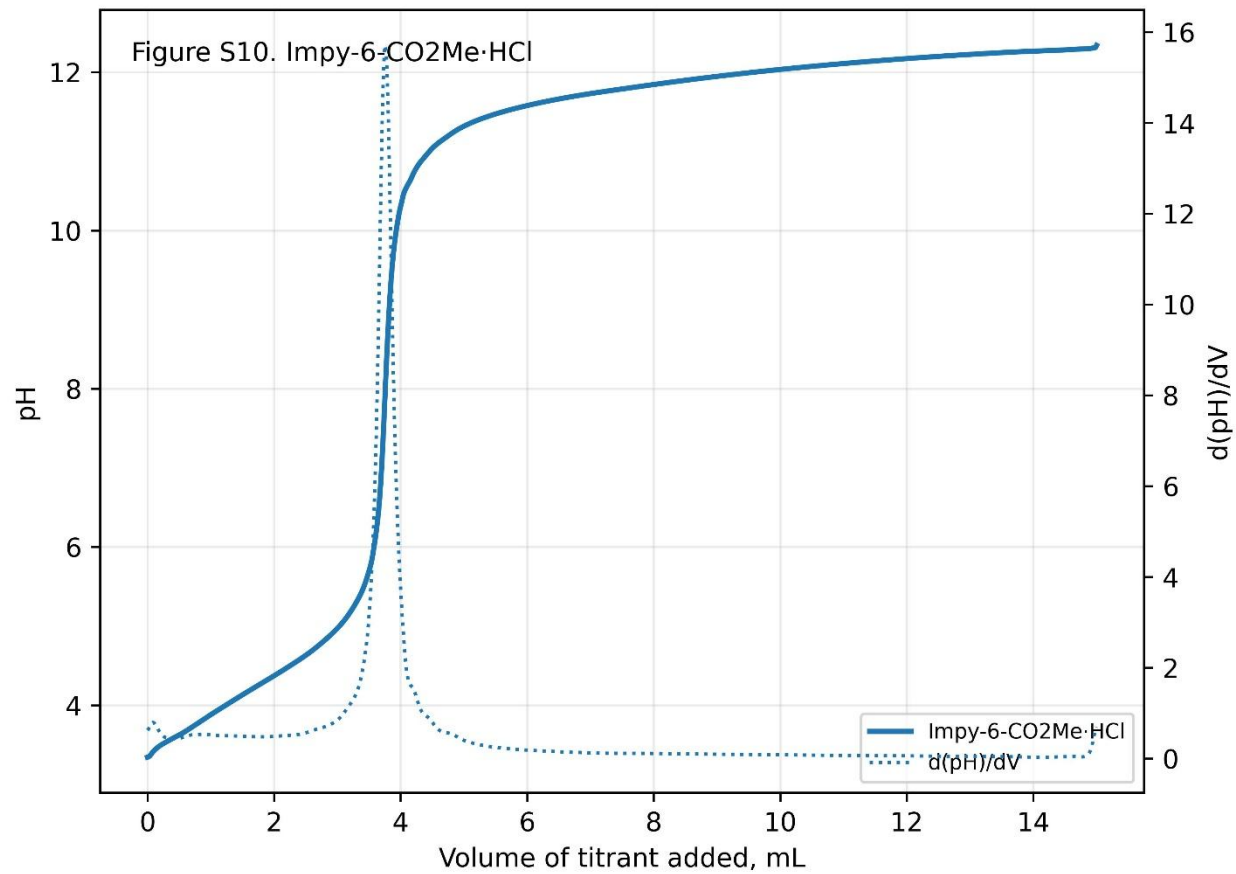
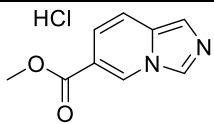
**Impy-1-CO<sub>2</sub>Me**



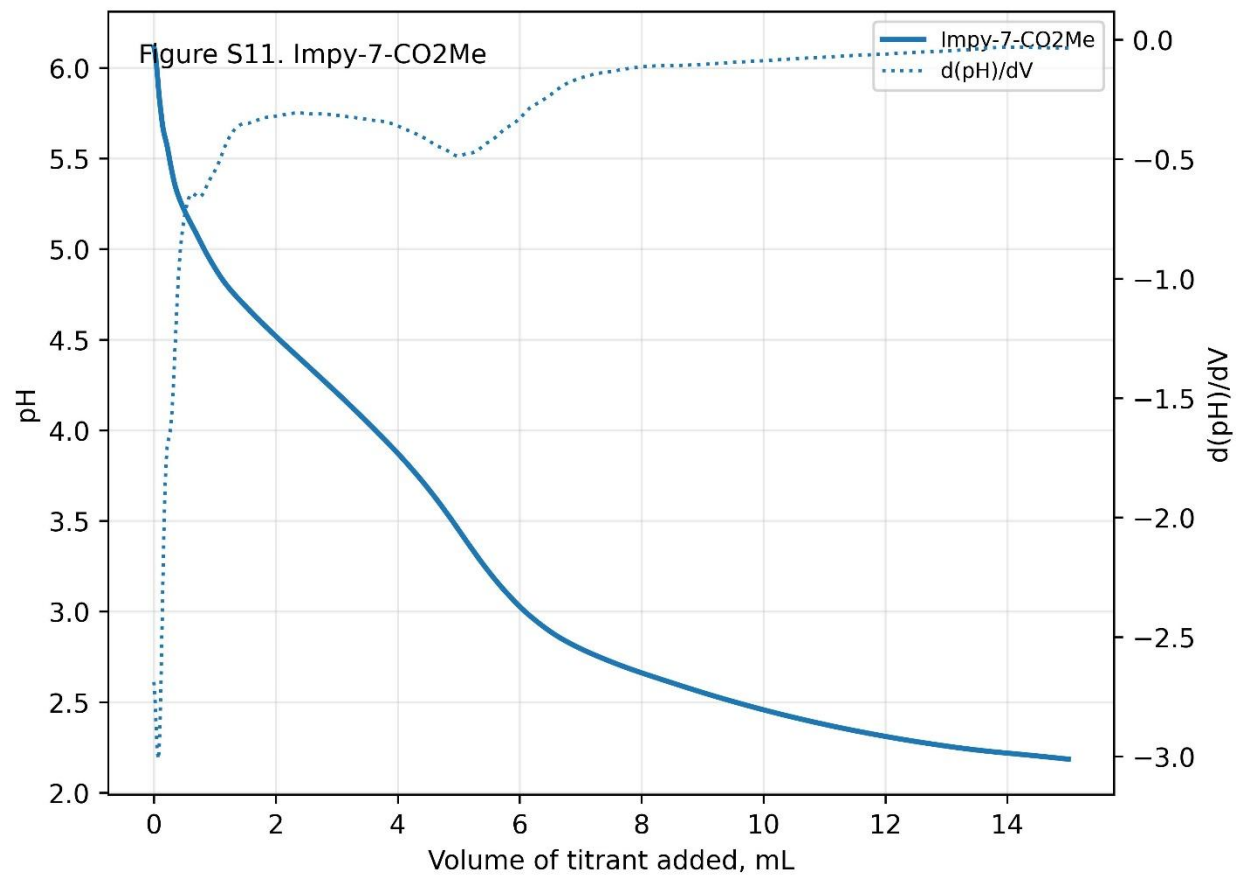
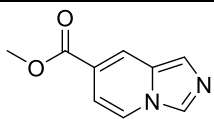
**Impy-3-CO<sub>2</sub>Et**



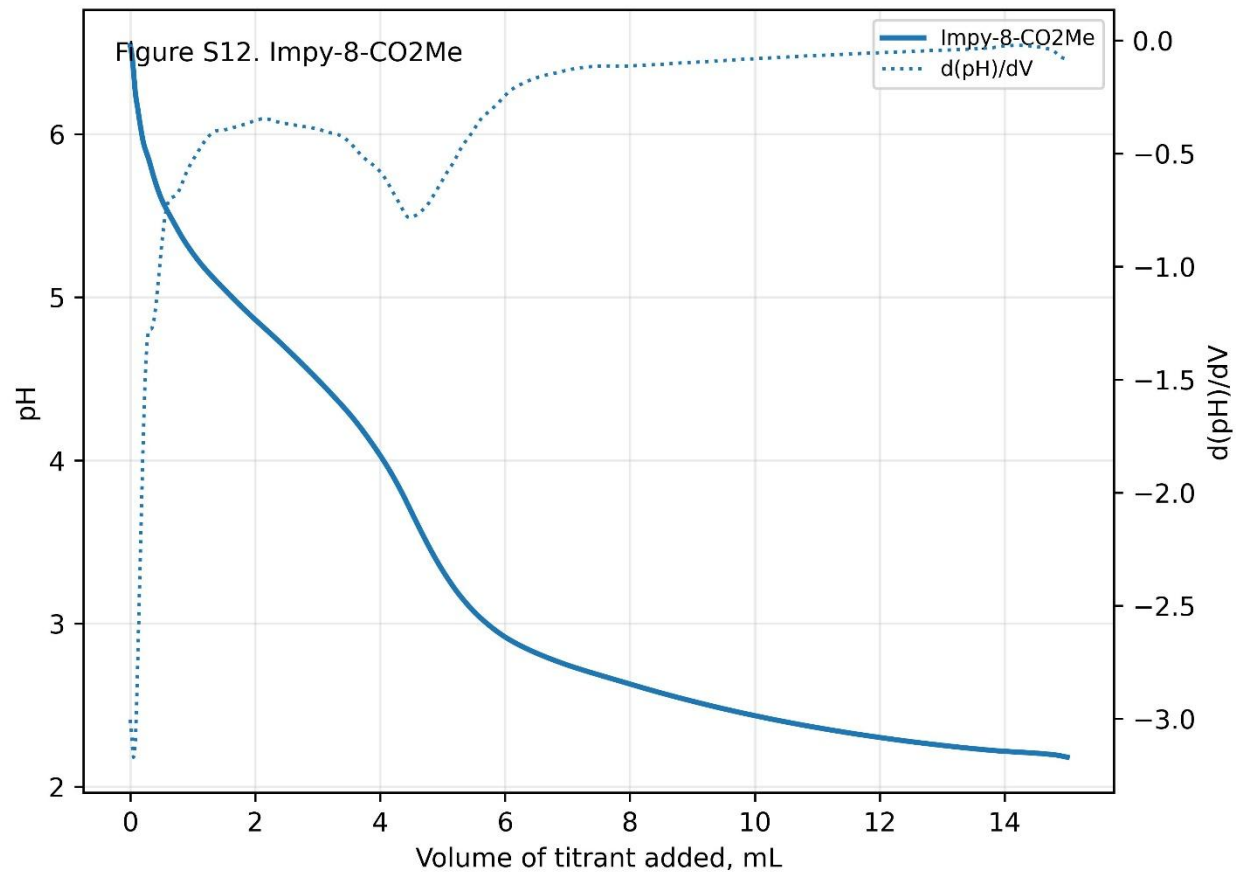
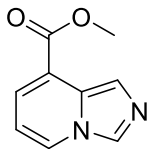
**Impy-5-CO<sub>2</sub>Me**



**Impy-6-CO<sub>2</sub>Me·HCl**



**Impy-7-CO<sub>2</sub>Me**



**Impy-8-CO<sub>2</sub>Me**